```
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* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  DEC 05   CASREACT(R) - Over 10 million reactions available
 NEWS  4  DEC 14   2006 MeSH terms loaded in MEDLINE/LMEDLINE
 NEWS  5  DEC 14   2006 MeSH terms loaded for MEDLINE file segment of TOXCENTER
 NEWS  6  DEC 14   CA/CAplus to be enhanced with updated IPC codes
 NEWS  7  DEC 21   IPC search and display fields enhanced in CA/CAplus with the
                   IPC reform
 NEWS  8  DEC 23   New IPC8 SEARCH, DISPLAY, and SELECT fields in USPATFULL/
                   USPAT2
 NEWS  9  JAN 13   IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
 NEWS 10  JAN 13   New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to
                   INPADOC
 NEWS 11  JAN 17   Pre-1988 INPI data added to MARPAT
 NEWS 12  JAN 17   IPC 8 in the WPI family of databases including WPIFV

 NEWS EXPRESS  JANUARY 03 CURRENT VERSION FOR WINDOWS IS V8.01,
               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
               V8.0 USERS CAN OBTAIN THE UPGRADE TO V8.01 AT
               http://download.cas.org/express/v8.0-Discover/

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  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006

=> file medline
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006
```

```
 FILE LAST UPDATED: 21 JAN 2006 (20060121/UP).  FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 will soon be available.  For details
 on the 2005 reload, enter HELP RLOAD at an arrow promt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate

=> s melanin
          7148 MELANIN
          6333 MELANINS
L1        9970 MELANIN
                 (MELANIN OR MELANINS)

=> s melanoma
         60502 MELANOMA
          9282 MELANOMAS
            80 MELANOMATA
             1 MELANOMATAS
L2       61483 MELANOMA
                 (MELANOMA OR MELANOMAS OR MELANOMATA OR MELANOMATAS)

=> s l2 and l1
L3        2328 L2 AND L1

=> s antibod?
L4      705098 ANTIBOD?

=> s l3 and l4
L5         198 L3 AND L4

=> s anti (W2) melanin
MISSING OPERATOR 'ANTI (W2'
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s anti (N2) melanin
MISSING OPERATOR 'ANTI (N2'
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s anti (2w) melanin
        589948 ANTI
             6 ANTIS
        589952 ANTI
                 (ANTI OR ANTIS)
          7148 MELANIN
          6333 MELANINS
          9970 MELANIN
                 (MELANIN OR MELANINS)
```

L6 7 ANTI (2W) MELANIN

=> s l6 and l2
L7 2 L6 AND L2

=> d ibib 1-2

L7 ANSWER 1 OF 2 MEDLINE on STN
ACCESSION NUMBER: 92335128 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1631018
TITLE: Response of transformed and normal mouse cell lines to **anti-melanin** compounds, hyperthermia, and radiation.
AUTHOR: Raaphorst G P; Azzam E I
CORPORATE SOURCE: Ottawa Regional Cancer Centre, Ontario, Canada.
SOURCE: Pigment cell research / sponsored by the European Society for Pigment Cell Research and the International Pigment Cell Society, (1992 Feb) 5 (1) 25-9.
Journal code: 8800247. ISSN: 0893-5785.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199208
ENTRY DATE: Entered STN: 19920904
Last Updated on STN: 19970203
Entered Medline: 19920820

L7 ANSWER 2 OF 2 MEDLINE on STN
ACCESSION NUMBER: 88107389 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3426925
TITLE: Radiation, heat and **anti-melanin** drug response of a transformed mouse embryo cell line with varying melanin content.
AUTHOR: Raaphorst G P; Azzam E I
CORPORATE SOURCE: Ottawa Regional Cancer Center, Ontario, Canada.
SOURCE: British journal of cancer, (1987 Nov) 56 (5) 622-4.
Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198803
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19880309

=> s l7 and l4
L8 0 L7 AND L4

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.90	2.11

FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006

FILE COVERS 1907 - 23 Jan 2006 VOL 144 ISS 5
FILE LAST UPDATED: 22 Jan 2006 (20060122/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

http://www.cas.org/infopolicy.html

```
=> s melanin
          9775 MELANIN
          7167 MELANINS
L9       11188 MELANIN
                 (MELANIN OR MELANINS)

=> s cancer or tumor or neoplas? or melanoma?
        267591 CANCER
         38666 CANCERS
        277754 CANCER
                 (CANCER OR CANCERS)
        359426 TUMOR
        142769 TUMORS
        405092 TUMOR
                 (TUMOR OR TUMORS)
        435881 NEOPLAS?
         30616 MELANOMA?
L10     690010 CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?

=> s l9 (l) l10
L11       1762 L9 (L) L10

=> s antibod?
L12     451938 ANTIBOD?

=> s l11 and l12
L13         60 L11 AND L12

=> s l3 (l) l9
PROXIMITY OPERATION NOT ALLOWED
Certain operators may not be nested in combination with other
operators.  A nested operator is valid only when it occurs at the same
level or above the operator outside the nested phrase as determined by
the following precedence list:

                  1.    Numeric
                  2.    (W), (NOTW), (A), (NOTA)
                  3.    (S), (NOTS)
                  4.    (P), (NOTP)
                  5.    (L), (NOTL)
                  6.    AND, NOT
                  7.    OR

For example, '(MONOCLONAL(W)ANTIBOD?)(L)ANTIGEN?' is valid since (W)
is above (L) on the precedence list.  However,
'((THIN(W)LAYER)(L)PHOSPHOLIPID#)(A)LACTONE#' is not valid since (L)
```

is below (A) on the precedence list. The only exception is the 'OR' operator. This operator may be used in combination with any other operator. For example, '(ATOMIC OR NUCLEAR)(W)REACTOR' is valid.

```
=> s l9 (l) l12
L14         190 L9 (L) L12

=> s l14 and l10
L15          59 L14 AND L10

=> s l14 and l13
L16          53 L14 AND L13

=> s l16 not py>2002
       3463589 PY>2002
L17          45 L16 NOT PY>2002

=> d ibib 1-3

L17  ANSWER 1 OF 45  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2001:711229  CAPLUS
DOCUMENT NUMBER:          136:4079
TITLE:                    Abnormal translocation of tyrosinase and
                          tyrosinase-related protein 1 in cutaneous melanocytes
                          of Hermansky-Pudlak syndrome and in melanoma cells
                          transfected with anti-sense HPS1 cDNA
AUTHOR(S):                Sarangarajan, Rangaprasad; Budev, Ashish; Zhao, Yang;
                          Gahl, William A.; Boissy, Raymond E.
CORPORATE SOURCE:         Department of Dermatology, University of Cincinnati,
                          Cincinnati, OH, USA
SOURCE:                   Journal of Investigative Dermatology (2001), 117(3),
                          641-646
                          CODEN: JIDEAE; ISSN: 0022-202X
PUBLISHER:                Blackwell Science, Inc.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          12    THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17  ANSWER 2 OF 45  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2000:597655  CAPLUS
DOCUMENT NUMBER:          133:249026
TITLE:                    Studies on epidermis reconstructed with and without
                          melanocytes: melanocytes prevent sunburn cell
                          formation but not appearance of DNA damaged cells in
                          fair-skinned caucasians
AUTHOR(S):                Cario-Andre, Muriel; Pain, Catherine; Gall, Yvon;
                          Ginestar, Jose; Nikaido, Osamu; Taieb, Alain
CORPORATE SOURCE:         Unite de Dermatologie, Universite Victor Segalen
                          Bordeaux II, Bordeaux, 33076, Fr.
SOURCE:                   Journal of Investigative Dermatology (2000), 115(2),
                          193-199
                          CODEN: JIDEAE; ISSN: 0022-202X
PUBLISHER:                Blackwell Science, Inc.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          45    THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17  ANSWER 3 OF 45  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2000:380955  CAPLUS
DOCUMENT NUMBER:          134:39063
TITLE:                    T311 - an anti-tyrosinase monoclonal antibody
```

```
                        for the detection of melanocytic lesions in paraffin
                        embedded tissues
AUTHOR(S):              Jungbluth, Achim A.; Iversen, Kristin; Coplan, Keren;
                        Kolb, Denise; Stockert, Elisabeth; Chen, Yao-Tseng;
                        Old, Lloyd J.; Busam, Klaus
CORPORATE SOURCE:       Ludwig Institute for Cancer Research at Memorial
                        Sloan-Kettering Cancer, New York, NY, 10021, USA
SOURCE:                 Pathology, Research and Practice (2000), 196(4),
                        235-242
                        CODEN: PARPDS; ISSN: 0344-0338
PUBLISHER:              Urban & Fischer Verlag
DOCUMENT TYPE:          Journal
LANGUAGE:               English
REFERENCE COUNT:        45    THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS
                              RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> d his

     (FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006)

     FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006
L1          9970 S MELANIN
L2         61483 S MELANOMA
L3          2328 S L2 AND L1
L4        705098 S ANTIBOD?
L5           198 S L3 AND L4
L6             7 S ANTI (2W) MELANIN
L7             2 S L6 AND L2
L8             0 S L7 AND L4

     FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006
L9         11188 S MELANIN
L10       690010 S CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?
L11         1762 S L9 (L) L10
L12       451938 S ANTIBOD?
L13           60 S L11 AND L12
L14          190 S L9 (L) L12
L15           59 S L14 AND L10
L16           53 S L14 AND L13
L17           45 S L16 NOT PY>2002

=> s in vivo
        413660 VIVO
             2 VIVOS
L18     413661 IN VIVO
                (VIVO OR VIVOS)

=> s l18 and l17
L19           3 L18 AND L17

=> d ibib 1-3

L19  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:       2000:597655  CAPLUS
DOCUMENT NUMBER:        133:249026
TITLE:                  Studies on epidermis reconstructed with and without
                        melanocytes: melanocytes prevent sunburn cell
                        formation but not appearance of DNA damaged cells in
                        fair-skinned caucasians
AUTHOR(S):              Cario-Andre, Muriel; Pain, Catherine; Gall, Yvon;
                        Ginestar, Jose; Nikaido, Osamu; Taieb, Alain
CORPORATE SOURCE:       Unite de Dermatologie, Universite Victor Segalen
```

Bordeaux II, Bordeaux, 33076, Fr.
SOURCE: Journal of Investigative Dermatology (2000), 115(2), 193-199
CODEN: JIDEAE; ISSN: 0022-202X
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:304007 CAPLUS
DOCUMENT NUMBER: 134:191455
TITLE: gp100 mRNA is more sensitive than tyrosinase mRNA for RT-PCR amplification to detect circulating melanoma cells in peripheral blood of melanoma patients
AUTHOR(S): Tsukamoto, K.; Ueda, M.; Hirata, S.; Osada, A.; Kitamura, R.; Takahashi, T.; Ichihashi, M.; Shimada, S.
CORPORATE SOURCE: Nakakoma, Tamaho, 1110 Shimokato, Department of Dermatology, Yamanashi Medical University, Yamanashi, Japan
SOURCE: Journal of Dermatological Science (2000), 23(2), 126-131
CODEN: JDSCEI; ISSN: 0923-1811
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1988:143024 CAPLUS
DOCUMENT NUMBER: 108:143024
TITLE: Cyclic AMP induces differentiation in vitro of human melanoma cells
AUTHOR(S): Giuffre, Laura; Schreyer, Magali; Mach, Jean Pierre; Carrel, Stefan
CORPORATE SOURCE: Ludwig Inst. Cancer Res., Epalinges, CH-1066, Switz.
SOURCE: Cancer (New York, NY, United States) (1988), 61(6), 1132-41
CODEN: CANCAR; ISSN: 0008-543X
DOCUMENT TYPE: Journal
LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006)

FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006
L1 9970 S MELANIN
L2 61483 S MELANOMA
L3 2328 S L2 AND L1
L4 705098 S ANTIBOD?
L5 198 S L3 AND L4
L6 7 S ANTI (2W) MELANIN
L7 2 S L6 AND L2
L8 0 S L7 AND L4

FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006
L9 11188 S MELANIN
L10 690010 S CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?

```
L11        1762 S L9 (L) L10
L12      451938 S ANTIBOD?
L13          60 S L11 AND L12
L14         190 S L9 (L) L12
L15          59 S L14 AND L10
L16          53 S L14 AND L13
L17          45 S L16 NOT PY>2002
L18      413661 S IN VIVO
L19           3 S L18 AND L17

=> s l17 and label?
        426929 LABEL?
L20           4 L17 AND LABEL?

=> d ibib 1-4

L20  ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1998:426503  CAPLUS
DOCUMENT NUMBER:          129:201389
TITLE:                    Comparative immunohistochemical estrogen receptor
                          analysis in primary and metastatic uveal melanoma
AUTHOR(S):                Makitie, Teemu; Tarkkanen, Ahti; Kivela, Tero
CORPORATE SOURCE:         Ophthalmic Pathology Laboratory, Department of
                          Ophthalmology, Helsinki University Central Hospital,
                          Hyks, FIN-00029, Finland
SOURCE:                   Graefe's Archive for Clinical and Experimental
                          Ophthalmology (1998), 236(6), 415-419
                          CODEN: GACODL; ISSN: 0721-832X
PUBLISHER:                Springer-Verlag
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          35    THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20  ANSWER 2 OF 4  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1994:188128  CAPLUS
DOCUMENT NUMBER:          120:188128
TITLE:                    The mouse brown (b) locus protein has dopachrome
                          tautomerase activity and is located in lysosomes in
                          transfected fibroblasts
AUTHOR(S):                Winder, Alison J.; Wittbjer, Anna; Rosengren, Evald;
                          Rorsman, Hans
CORPORATE SOURCE:         Sir William Dunn Sch. Pathol., Univ. Oxford Rd,
                          Oxford, OX1 3RE, UK
SOURCE:                   Journal of Cell Science (1993), 106(1), 153-66
                          CODEN: JNCSAI; ISSN: 0021-9533
DOCUMENT TYPE:            Journal
LANGUAGE:                 English

L20  ANSWER 3 OF 4  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1992:4874  CAPLUS
DOCUMENT NUMBER:          116:4874
TITLE:                    Monoclonal antibody against a melanosomal
                          protein in melanotic and amelanotic human melanoma
                          cells
AUTHOR(S):                McEwan, Max; Parsons, Peter G.; Moss, Denis J.;
                          Burrows, Scott; Stenzel, Debbie; Bishop, Chris J.;
                          Strutton, Geoffrey M.
CORPORATE SOURCE:         Queensland Inst. Medical Res., Herston, 4006,
                          Australia
SOURCE:                   Pigment Cell Research (1989), 2(1), 1-7
                          CODEN: PCREEA; ISSN: 0893-5785
DOCUMENT TYPE:            Journal
```

LANGUAGE: English

L20 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1979:609110 CAPLUS
DOCUMENT NUMBER: 91:209110
TITLE: Demonstration and isolation of murine melanoma-associated antigenic surface proteins
AUTHOR(S): Gersten, Douglas M.; Marchalonis, John J.
CORPORATE SOURCE: Frederick Cancer Res. Cent., Natl. Cancer Inst., Frederick, MD, 21701, USA
SOURCE: Biochemical and Biophysical Research Communications (1979), 90(3), 1015-24
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English

=> d abs 3

L20 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
AB BALB/c mice were immunized with tyrosinase, partially purified in 2 stages from a human **melanoma** cell line. A hybridoma was obtained which produced monoclonal **antibody** (MoAb 1C11) reactive with 8/10 **melanoma** cell lines and 10/10 primary cultures of human melanocytes, neval cells, and **melanomas**. Immunoreactivity correlated to a certain extent with tyrosinase activity but not with **melanin** content. No crossreactivity was obtained with neuroblastoma, medulloblastoma, fibroblasts, keratinocytes, lymphoid cells, or murine **melanomas**. Purification of the antigen directly from cell lysates with a MoAb 1C11 CNBr-Sepharose affinity column gave a green-brown protein of 56 kDa with no detectable tyrosinase activity. This protein was therefore different from 60 kDa active tyrosinase, identified by enzyme activity and Western blotting with a MoAb derived previously (MoAb 5C12). Unlike 5C12, 1C11 reactivity was not destroyed by pretreatment of the antigen with periodate. Immunogold **labeling** showed that the 1C11-reactive antigen was associated with melanosomes, and there was close correlation between 5C12 and 1C11 reactivity in resistance to trypsin and in staining various melanocytic cell populations. MoAb 1C11 may therefore recognize a polypeptide epitope in a mol. closely linked to **melanin** biosynthesis.

=> 6D2
6D2 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s 6D2
L21 46 6D2

=> d his

(FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006)

FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006
L1 9970 S MELANIN
L2 61483 S MELANOMA
L3 2328 S L2 AND L1
L4 705098 S ANTIBOD?
L5 198 S L3 AND L4
L6 7 S ANTI (2W) MELANIN
L7 2 S L6 AND L2

```
L8            0 S L7 AND L4

     FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006
L9        11188 S MELANIN
L10      690010 S CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?
L11        1762 S L9 (L) L10
L12      451938 S ANTIBOD?
L13          60 S L11 AND L12
L14         190 S L9 (L) L12
L15          59 S L14 AND L10
L16          53 S L14 AND L13
L17          45 S L16 NOT PY>2002
L18      413661 S IN VIVO
L19           3 S L18 AND L17
L20           4 S L17 AND LABEL?
L21          46 S 6D2

=> s l21 and l10
L22           2 L21 AND L10

=> d ibib 1-2

L22  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2004:888105  CAPLUS
DOCUMENT NUMBER:          142:2821
TITLE:                    Dead cells in melanoma tumors
                          provide abundant antigen for targeted delivery of
                          ionizing radiation by a mAb to melanin
AUTHOR(S):                Dadachova, Ekaterina; Nosanchuk, Joshua D.; Shi, Li;
                          Schweitzer, Andrew D.; Frenkel, Annie; Nosanchuk,
                          Jerome S.; Casadevall, Arturo
CORPORATE SOURCE:         Department of Nuclear Medicine, Albert Einstein
                          College of Medicine, Bronx, NY, 10461, USA
SOURCE:                   Proceedings of the National Academy of Sciences of the
                          United States of America (2004), 101(41), 14865-14870
                          CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER:                National Academy of Sciences
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          55    THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22  ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1993:577867  CAPLUS
DOCUMENT NUMBER:          119:177867
TITLE:                    A heparan sulfate proteoglycan in developing avian
                          axonal tracts
AUTHOR(S):                Halfter, Willi
CORPORATE SOURCE:         Dep. Neurobiol., Univ. Pittsburgh, Pittsburgh, PA,
                          15261, USA
SOURCE:                   Journal of Neuroscience (1993), 13(7), 2863-73
                          CODEN: JNRSDS; ISSN: 0270-6474
DOCUMENT TYPE:            Journal
LANGUAGE:                 English


=> d kwic 2

L22  ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2006 ACS on STN
AB   . . . immunized with embryonic chick retina basal lamina (clones 3A 12,
     3A3, and 9E 10) and embryonic chick optic tract (clone 6D2).
     Cross-reactivity of all 4 antibodies were directed to the same antigen.
     Antibodies to heparan sulfate proteoglycan from embryonic chick muscle or
```

EHS mouse **tumor** (perlecan) did not cross-react with the neuronal heparan sulfate proteoglycan, suggesting that the 2 proteoglycans are not related. In Western. . .

```
=> s anti (2W) melanin
        393809 ANTI
             9 ANTIS
        393816 ANTI
                 (ANTI OR ANTIS)
          9775 MELANIN
          7167 MELANINS
         11188 MELANIN
                 (MELANIN OR MELANINS)
L23         14 ANTI (2W) MELANIN

=> s l23 and antibod?
        451938 ANTIBOD?
L24          7 L23 AND ANTIBOD?

=> d ibib 1-7

L24  ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2004:888105  CAPLUS
DOCUMENT NUMBER:          142:2821
TITLE:                    Dead cells in melanoma tumors provide abundant antigen
                          for targeted delivery of ionizing radiation by a mAb
                          to melanin
AUTHOR(S):                Dadachova, Ekaterina; Nosanchuk, Joshua D.; Shi, Li;
                          Schweitzer, Andrew D.; Frenkel, Annie; Nosanchuk,
                          Jerome S.; Casadevall, Arturo
CORPORATE SOURCE:         Department of Nuclear Medicine, Albert Einstein
                          College of Medicine, Bronx, NY, 10461, USA
SOURCE:                   Proceedings of the National Academy of Sciences of the
                          United States of America (2004), 101(41), 14865-14870
                          CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER:                National Academy of Sciences
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          55    THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24  ANSWER 2 OF 7  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2004:654728  CAPLUS
DOCUMENT NUMBER:          141:186978
TITLE:                    Radiolabeled antibodies for treatment of
                          tumors
INVENTOR(S):              Dadachova, Ekaterina; Nosanchuk, Joshua D.;
                          Casadevall, Arturo
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 23 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     ---------------      ----   --------    --------------------     --------
     US 2004156780         A1    20040812    US 2004-775869           20040210
PRIORITY APPLN. INFO.:                       US 2003-446684P      P   20030211

L24  ANSWER 3 OF 7  CAPLUS  COPYRIGHT 2006 ACS on STN
```

ACCESSION NUMBER: 2004:339308 CAPLUS
DOCUMENT NUMBER: 141:136788
TITLE: Production of melanin by Aspergillus fumigatus
AUTHOR(S): Youngchim, Sirida; Morris-Jones, Rachael; Hay, Roderick J.; Hamilton, Andrew J.
CORPORATE SOURCE: Dermatology Department, St Johns Institute of Dermatology, Guy's Hospital, Kings and St Thomas' Medical Schools, London, UK
SOURCE: Journal of Medical Microbiology (2004), 53(3), 175-181
CODEN: JMMIAV; ISSN: 0022-2615
PUBLISHER: Society for General Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:639215 CAPLUS
DOCUMENT NUMBER: 137:307123
TITLE: Histoplasma capsulatum synthesizes melanin-like pigments in vitro and during mammalian infection
AUTHOR(S): Nosanchuk, Joshua D.; Gomez, Beatriz L.; Youngchim, Sirida; Diez, Soraya; Aisen, Philip; Zancope-Oliveira, Rosely M.; Restrepo, Angela; Casadevall, Arturo; Hamilton, Andrew J.
CORPORATE SOURCE: Department of Medicine, Albert Einstein College of Medicine, Bronx, NY, 10461, USA
SOURCE: Infection and Immunity (2002), 70(9), 5124-5131
CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:457194 CAPLUS
DOCUMENT NUMBER: 133:85156
TITLE: Human melanin concentrating hormone receptor MCH1 and cDNA and diagnostic and therapeutic uses thereof
INVENTOR(S): Salon, John A.; Laz, Thomas M.; Nagorny, Raisa; Wilson, Amy E.
PATENT ASSIGNEE(S): Synaptic Pharmaceutical Corporation, USA
SOURCE: PCT Int. Appl., 173 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000039279	A2	20000706	WO 1999-US31169	19991230
WO 2000039279	A3	20001102		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6221613	B1	20010424	US 1998-224426	19981231
CA 2358687	AA	20000706	CA 1999-2358687	19991230
AU 2000033430	A5	20000731	AU 2000-33430	19991230
AU 774398	B2	20040624		
EP 1141020	A2	20011010	EP 1999-969993	19991230
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002533116	T2	20021008	JP 2000-591172	19991230
US 6221616	B1	20010424	US 2000-478601	20000106
US 6291195	B1	20010918	US 2000-478602	20000106
US 2002111306	A1	20020815	US 2001-885478	20010620
US 6723552	B2	20040420		
US 2003082623	A1	20030501	US 2001-899732	20010705
US 2003077701	A1	20030424	US 2001-29314	20011220
US 2004038855	A1	20040226	US 2003-341751	20030114
US 2004248173	A1	20041209	US 2004-825581	20040415

PRIORITY APPLN. INFO.:

US 1998-224426	A2	19981231
WO 1999-US31169	W	19991230
US 2000-610635	A2	20000705
US 2001-885478	A1	20010620
US 2001-899732	A1	20010705

L24 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:408610 CAPLUS
DOCUMENT NUMBER: 131:180636
TITLE: Structure and function of human prepro-orexin gene
AUTHOR(S): Sakurai, Takeshi; Moriguchi, Takashi; Furuya, Keiko; Kajiwara, Noriko; Nakamura, Toshiaki; Yanagisawa, Masashi; Goto, Katsutoshi
CORPORATE SOURCE: Institute of Basic Medical Sciences, University of Tsukuba, Tsukuba, 305-8575, Japan
SOURCE: Journal of Biological Chemistry (1999), 274(25), 17771-17776
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1991:465553 CAPLUS
DOCUMENT NUMBER: 115:65553
TITLE: Mammalian melanin-concentrating hormones (MCHs) and methods of treatment using same
INVENTOR(S): Vaughan, Joan; Fischer, Wolfgang Hermann; Rivier, Jean Edouard; Nahon, Jean Louis Marie; Presse, Francoise Genevieve; Vale, Wylie Walker, Jr.
PATENT ASSIGNEE(S): Salk Institute for Biological Studies, USA
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9011295	A1	19901004	WO 1990-US1492	19900320
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
US 5049655	A	19910917	US 1989-326984	19890322

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     CA 2046900           AA    19900923    CA 1990-2046900         19900320
     CA 2046900           C     20000822
     EP 464105            A1    19920108    EP 1990-905279          19900320
     EP 464105            B1    19960814
         R:  AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE
     JP 04503812          T2    19920709    JP 1990-505271          19900320
     JP 2944202           B2    19990830
     AT 141288            E     19960815    AT 1990-905279          19900320
     US 5449766           A     19950912    US 1994-208531          19940309
     US 5530095           A     19960625    US 1995-447613          19950523
PRIORITY APPLN. INFO.:                       US 1989-326984      A   19890322
                                             WO 1990-US1492      W   19900320
                                             US 1991-733660      B3  19910722
                                             US 1994-208531      A3  19940309
OTHER SOURCE(S):          MARPAT 115:65553


=> d his

     (FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006)

     FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006
L1          9970 S MELANIN
L2         61483 S MELANOMA
L3          2328 S L2 AND L1
L4        705098 S ANTIBOD?
L5           198 S L3 AND L4
L6             7 S ANTI (2W) MELANIN
L7             2 S L6 AND L2
L8             0 S L7 AND L4

     FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006
L9         11188 S MELANIN
L10       690010 S CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?
L11         1762 S L9 (L) L10
L12       451938 S ANTIBOD?
L13           60 S L11 AND L12
L14          190 S L9 (L) L12
L15           59 S L14 AND L10
L16           53 S L14 AND L13
L17           45 S L16 NOT PY>2002
L18       413661 S IN VIVO
L19            3 S L18 AND L17
L20            4 S L17 AND LABEL?
L21           46 S 6D2
L22            2 S L21 AND L10
L23           14 S ANTI (2W) MELANIN
L24            7 S L23 AND ANTIBOD?

=> s l24 and l10
L25           3 L24 AND L10

=> de ibib 1-3
DE IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d ibib 1-3

L25  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2004:888105  CAPLUS
DOCUMENT NUMBER:          142:2821
```

TITLE: Dead cells in **melanoma tumors** provide abundant antigen for targeted delivery of ionizing radiation by a mAb to melanin
AUTHOR(S): Dadachova, Ekaterina; Nosanchuk, Joshua D.; Shi, Li; Schweitzer, Andrew D.; Frenkel, Annie; Nosanchuk, Jerome S.; Casadevall, Arturo
CORPORATE SOURCE: Department of Nuclear Medicine, Albert Einstein College of Medicine, Bronx, NY, 10461, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2004), 101(41), 14865-14870 CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:654728 CAPLUS
DOCUMENT NUMBER: 141:186978
TITLE: Radiolabeled **antibodies** for treatment of **tumors**
INVENTOR(S): Dadachova, Ekaterina; Nosanchuk, Joshua D.; Casadevall, Arturo
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 23 pp. CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004156780	A1	20040812	US 2004-775869		20040210
PRIORITY APPLN. INFO.:			US 2003-446684P	P	20030211

L25 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:465553 CAPLUS
DOCUMENT NUMBER: 115:65553
TITLE: Mammalian melanin-concentrating hormones (MCHs) and methods of treatment using same
INVENTOR(S): Vaughan, Joan; Fischer, Wolfgang Hermann; Rivier, Jean Edouard; Nahon, Jean Louis Marie; Presse, Francoise Genevieve; Vale, Wylie Walker, Jr.
PATENT ASSIGNEE(S): Salk Institute for Biological Studies, USA
SOURCE: PCT Int. Appl., 47 pp. CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9011295	A1	19901004	WO 1990-US1492	19900320
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
US 5049655	A	19910917	US 1989-326984	19890322
CA 2046900	AA	19900923	CA 1990-2046900	19900320
CA 2046900	C	20000822		
EP 464105	A1	19920108	EP 1990-905279	19900320
EP 464105	B1	19960814		

R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE

JP 04503812	T2	19920709	JP 1990-505271	19900320
JP 2944202	B2	19990830		
AT 141288	E	19960815	AT 1990-905279	19900320
US 5449766	A	19950912	US 1994-208531	19940309
US 5530095	A	19960625	US 1995-447613	19950523
PRIORITY APPLN. INFO.:			US 1989-326984 A	19890322
			WO 1990-US1492 W	19900320
			US 1991-733660 B3	19910722
			US 1994-208531 A3	19940309

OTHER SOURCE(S): MARPAT 115:65553

=> d kwic 3

L25 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN

AB . . . characterized. The MCH and related peptides, formed from MCH precursors, are useful for treating skin disorders, suppressing proliferation of skin **tumor** (e.g. **melanoma**) cells in mammals, and modulating ACTH secretion. Also disclosed are the amino acid sequences and cDNA nucleotide sequences of rat. . .

ST rat melanin concg hormone; human melanin concg hormone; ACTH generation melanin concg hormone; skin **neoplasm** melanin cong hormone

IT **Antibodies**
RL: PROC (Process)
(to melanin-concentrating hormone of salmon, production of, for rat melanin-concentrating hormone purification)

IT Globins
RL: BIOL (Biological study)
(α-subunits, conjugates, with melanin-concentrating hormone of salmon, for **antibody** production for rat melanin-concentrating hormone purification)

IT Proteins, specific or class
RL: BIOL (Biological study)
(A, conjugates, with Sepharose CL-4B and **anti**-salmon **melanin**-concentrating hormone **antibody**, for rat melanin-concentrating hormone purification)

IT 87218-84-6D, Melanin-concentrating hormone (Oncorhynchus keta), α-globin conjugates
RL: BIOL (Biological study)
(for **antibody** production for rat melanin-concentrating hormone purification)

IT 61970-08-9D, Sepharose CL-4B, conjugates with protein A and **anti**-salmon **melanin**-concentrating hormone **antibodies**
RL: BIOL (Biological study)
(in rat melanin-concentrating hormone purification)

=> file pctfull

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	61.54	63.65
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-2.25	-2.25

FILE 'PCTFULL' ENTERED AT 14:16:40 ON 23 JAN 2006

FILE LAST UPDATED: 3 JAN 2006 <20060103/UP>
MOST RECENT UPDATE WEEK: 200552 <200552/EW>
FILE COVERS 1978 TO DATE

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>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

>>> UPDATING DELAYED DUE TO DELIVERY FORMAT CHANGES. <<<

>>> NEW IPC8 DATA AND FUNCTIONALITY NOT YET AVAILABLE IN THIS FILE.
    USE IPC7 FORMAT FOR SEARCHING THE IPC. WATCH THIS SPACE FOR FURTHER
    DEVELOPMENTS AND SEE OUR NEWS SECTION FOR FURTHER INFORMATION
    ABOUT THE IPC REFORM <<<

=> d his

     (FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006)

     FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006
L1          9970 S MELANIN
L2         61483 S MELANOMA
L3          2328 S L2 AND L1
L4        705098 S ANTIBOD?
L5           198 S L3 AND L4
L6             7 S ANTI (2W) MELANIN
L7             2 S L6 AND L2
L8             0 S L7 AND L4

     FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006
L9         11188 S MELANIN
L10       690010 S CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?
L11         1762 S L9 (L) L10
L12       451938 S ANTIBOD?
L13           60 S L11 AND L12
L14          190 S L9 (L) L12
L15           59 S L14 AND L10
L16           53 S L14 AND L13
L17           45 S L16 NOT PY>2002
L18       413661 S IN VIVO
L19            3 S L18 AND L17
L20            4 S L17 AND LABEL?
L21           46 S 6D2
L22            2 S L21 AND L10
L23           14 S ANTI (2W) MELANIN
L24            7 S L23 AND ANTIBOD?
L25            3 S L24 AND L10

     FILE 'PCTFULL' ENTERED AT 14:16:40 ON 23 JAN 2006

=> s anti (2w) melanin
        167501 ANTI
           165 ANTIS
        167532 ANTI
                  (ANTI OR ANTIS)
          2796 MELANIN
           190 MELANINS
          2854 MELANIN
                  (MELANIN OR MELANINS)
L26          6 ANTI (2W) MELANIN

=> s l26 and antibod?
         84196 ANTIBOD?
L27          1 L26 AND ANTIBOD?

=> d ibib

L27    ANSWER 1 OF 1     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:       2004048547 PCTFULL  ED 20040615  EW 200424
```

TITLE (ENGLISH): INTERMEDIN AND ITS USES
TITLE (FRENCH): INTERMEDINE ET SES UTILISATIONS
INVENTOR(S): HSU, Sheau, Yu Teddy, 2038 Santa Cruz Avenue, Menlo Park, CA 94025, US
PATENT ASSIGNEE(S): THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, 1705 El Camino Real, Palo Alto, CA 94306-1106, US [US, US]
AGENT: SHERWOOD, Pamela J.$, BOZICEVIC, FIELD & FRANCIS LLP, 200 Middlefield Road, Suite 200, Menlo Park, CA 94025$, US
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004048547	A2	20040610

DESIGNATED STATES
W: AU CA JP
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
APPLICATION INFO.: WO 2003-US37968 A 20031126
PRIORITY INFO.: US 2002-60/429,327 20021126

=> s l26 and (cancer? or tumor? or neoplas?
UNMATCHED LEFT PARENTHESIS 'AND (CANCER?'
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=> s l26 and (cancer? or tumor? or neoplas?)
74539 CANCER?
62442 TUMOR?
21534 NEOPLAS?
L28 3 L26 AND (CANCER? OR TUMOR? OR NEOPLAS?)

=> d ibib 1-3

L28 ANSWER 1 OF 3 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2004087128 PCTFULL ED 20041019 EW 200442
TITLE (ENGLISH): METHYL-Β-ORCINOLCARBOXYLATE FROM LICHEN (EVERNIASTRUM CIRRHATUM) FOR USE FOR THE TREATMENT OF FUNGAL INFECTIONS AND **CANCER**
TITLE (FRENCH): METHYL-BETA-ORCINOL-CARBOXYLATE TIRE DU LICHEN EVERNIASTRUM CIRRHATUM DESTINE AU TRAITEMENT D'INFECTIONS FONGIQUES ET DU **CANCER**
INVENTOR(S): KHANUJA, Suman, Preet, Singh, Central Institute Of Medicinal And Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar Pradesh, IN;
TIRUPPADIRIPULIYUR, Ranganathan, Santha, Kumar, Central Institute of Medicinal and Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar Pradesh, IN;
GUPTA, Vivek, Kumar, Central Institute of Medicinal and Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar Pradesh, IN;
CHAND, Preeti, Central Institute of Medicinal and Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar Pradesh, IN;
GARG, Ankur, Central Institute of Medicinal and Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar Pradesh, IN;
SRIVASTAVA, Santosh, Kumar, Central Institute of Medicinal and Aromatic Plants, P.O. CIMAP, Lucknow 226

015, Uttar Pradesh, IN;
VERMA, Subash, Chandra, Central Institute of Medicinal and Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar Pradesh, IN;
SAIKIA, Dharmendra, Central Institute of Medicinal and Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar Pradesh, IN;
DAROKAR, Mahendra, Pandurang, Central Institute of Medicinal and Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar Pradesh, IN;
SHASANY, Ajit, Kumar, Central Institute of Medicinal and Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar Pradesh, IN;
PAL, Anirban, Central Institute of Medicinal and Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar Pradesh, IN

PATENT ASSIGNEE(S): COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH, Rafi Marg, New Delhi 110 001, IN [IN, IN]

AGENT: SUBRAMANIAM, Hariharan$, Subramaniam, Nataraj & Associates, E-556 Greater Kailash II, New Delhi 110 048$, IN

LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004087128	A1	20041014

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW
RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2003-IN97 A 20030331

L28 ANSWER 2 OF 3 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2004048547 PCTFULL ED 20040615 EW 200424
TITLE (ENGLISH): INTERMEDIN AND ITS USES
TITLE (FRENCH): INTERMEDINE ET SES UTILISATIONS
INVENTOR(S): HSU, Sheau, Yu Teddy, 2038 Santa Cruz Avenue, Menlo Park, CA 94025, US

PATENT ASSIGNEE(S): THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, 1705 El Camino Real, Palo Alto, CA 94306-1106, US [US, US]

AGENT: SHERWOOD, Pamela J.$, BOZICEVIC, FIELD & FRANCIS LLP, 200 Middlefield Road, Suite 200, Menlo Park, CA 94025$, US

LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004048547	A2	20040610

DESIGNATED STATES
W: AU CA JP
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU

MC NL PT RO SE SI SK TR
APPLICATION INFO.: WO 2003-US37968 A 20031126
PRIORITY INFO.: US 2002-60/429,327 20021126

L28 ANSWER 3 OF 3 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2003035167 PCTFULL ED 20030512 EW 200318
TITLE (ENGLISH): DEVICE AND METHOD FOR CONTROLLED DELIVERY OF ACTIVE SUBSTANCE INTO THE SKIN
TITLE (FRENCH): DISPOSITIF ET PROCEDE DE LIBERATION CONTROLEE D'UNE SUBSTANCE ACTIVE DANS LA PEAU
INVENTOR(S): MAVOR, Daniela, 36 Striker Street, 62006 Tel Aviv, IL [IL, IL];
NITZAN, Zvi, 70 Ha'ilanot Street, 44925 Zofit, IL [IL, IL];
TAMARKIN, Dov, 537 Har Hila Street, 91708 Maccabim, IL [IL, IL];
ARBEL, Giora, 5 David Hamelech Street, 44430 Kfar Saba, IL [IL, IL];
HAREL, Nurit, 5 Benayahu Street, 69084 Tel Aviv, IL [IL, IL];
GROSS, Yossi, Moshav Mazor 205, 73160 Moshav Mazor, IL [IL, IL]
PATENT ASSIGNEE(S): POWER PAPER LTD, P.O.Box 12, 49910 Kibbutz Einat, IL [IL, IL], for all designates States except US;
MAVOR, Daniela, 36 Striker Street, 62006 Tel Aviv, IL [IL, IL], for US only;
NITZAN, Zvi, 70 Ha'ilanot Street, 44925 Zofit, IL [IL, IL], for US only;
TAMARKIN, Dov, 537 Har Hila Street, 91708 Maccabim, IL [IL, IL], for US only;
ARBEL, Giora, 5 David Hamelech Street, 44430 Kfar Saba, IL [IL, IL], for US only;
HAREL, Nurit, 5 Benayahu Street, 69084 Tel Aviv, IL [IL, IL], for US only;
GROSS, Yossi, Moshav Mazor 205, 73160 Moshav Mazor, IL [IL, IL], for US only
AGENT: REINHOLD COHN AND PARTNERS$, P.O.B. 4060, 61040 Tel Aviv$, IL
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2003035167	A2	20030501

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2002-IL849 A 20021023
PRIORITY INFO.: US 2001-60/330,526 20011024
US 2002-60/401,771 20020808

=> s WO 199011295/pn
L29 1 WO 199011295/PN

(WO9011295/PN)

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=> s melanin and l29
          2796 MELANIN
           190 MELANINS
          2854 MELANIN
                 (MELANIN OR MELANINS)
L30          1 MELANIN AND L29

=> s l30 and antibod?
         84196 ANTIBOD?
L31          1 L30 AND ANTIBOD?

=> s cancer? or tumor? or neoplas?
         74539 CANCER?
         62442 TUMOR?
         21534 NEOPLAS?
L32      93014 CANCER? OR TUMOR? OR NEOPLAS?

=> s l32 and l31
L33          1 L32 AND L31

=> d kwic

L33    ANSWER 1 OF 1     PCTFULL   COPYRIGHT 2006 Univentio on STN
TIEN   MELANIN-CONCENTRATING HORMONES AND METHODS OF TREATMENT USING
       SAME
PI     WO 9011295          A1 19901004
ABEN   Mammalian melanin-concentrating hormone (MCH) is isolated from
       rat tissue, purified and
       characterized. These MCH peptides are useful for treating skin
       disorders, for suppressing the
       proliferation of skin tumor cells, such as melanomas in
       mammals, and for modulating the secretion of
       ACTH. Generally, peptides are provided which have formula. . . are
       thought to be formed from the MCH precursors, are the peptides with the
       sequence
       H-Glu-Ile-Gly-Asp-Glu-Glu-Asn-Ser-Ala-Lys-Phe-Pro-Ile-NH2, which is
       cross-reactive with antibodies
       against alpha-MSH and CRF, and the peptides with the sequence
       H-Gly-XNGE-Phe-Pro-Ala-Glu-Asn-Gly-Val-Gln-Asn-Thr-Glu-Ser-Thr-Gln-Glu-
       OH, wherein XNGE is
       Pro-Ala-Val or Ser-Val-Ala, which is cross-reactive with
       antibodies against GRF.
ABFR .  . . caracterisee. Ces peptides de MCH sont utiles pour traiter des
       troubles de la
       peau, pour supprimer la proliferation de cellules tumorales de
       la peau, telles que les melanomes
       chez les mammiferes, et pour moduler la secretion de ACTH. En general,
       les. . .

DETD   MELANIN-CONCENTRATING HORNONES
       AND METHODS OF TREATMMff USING SAME
       This invention relates to hormones for
       concentrating melanin in mammals and to methods of
       treating mammals using such hormones,
       BACKGROUND OF THE INVENTION
       A cyclic heptadecapeptide which induces
       melanosome aggregation within fish. . .

       et al., Nature, 305, 321-323 (1983), and it was named
         melanin concentrating hormone (MCH). Fish MCH has been
       reported to have the opposite effect, i.e., causing
```

dispersal of melanosomes, in amphibians, Wilkes, B.. . .
. . .
mammals to lighten skin color, as by local or topical application. It is also useful to suppress the proliferation of certain skin **tumor** cells, such as melanomas, when suitably applied as by topical application or the like. It is also found that mammalian MCH can. . .
. . .
at position 144 of the MCH precursors would provide the NH2 group of the C-terminal amide of NEI. It has been found that **antibodies** against human alpha-MSH (i.e., alpha]melanocyte stimulating hormone) and human CRF (corticotropin-releasing factor) cross]react with NEI, with the anti-alpha-MSH **antibodies** recognizing an epitope including the N-terminus of NEI and the anti-CRF **antibodies** recognizing an epitope including the C-terminus of NEI, It is thought that NEI has a biological function in vivo-,
The sequences of the NGE's correspond to the sequences of amino acids 110 - 128 of the MCH precursors (see Tables 1 and 2, below). **Antibodies** against human GRF (growth hormone releasing factor) cross]react with NGE, as suggested by our discovery of the close homology between the sequence Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu. . .

NEI is useful, in the process of making anti-alpha-MSH or anti]CRF monoclonal **antibody**]secreting hybridomas, as an immunogen for obtaining anti-alpha-MSH or anti-CRF **antibody**]producing splenocytes or lymphocytes and as an antigen for screening cultures of hybridomas for those which include hybridomas that make anti-MSH or anti-CRF **antibodies**. Similarly, NGE is useful in the process of making anti-GRF monoclonal **antibody**-secreting hybridomas. Monoclonal **antibodies** made by such hybridomas are useful for assaying for alpha]MSH, CRF or GRF by standard immunoassay methods.

Further, such a monoclonal **antibody** made with NEI or NGE as the immunogen, when used in a standard immunoaassay procedure in conjunction with a second monoclonal **antibody**, which recognizes an epitope of alpha-MSH, CRF or GRF different from the epitope recognized by the monoclonal **antibody** made with NEI or NGE as the immunogen, can be used to confirm that a peptide detected in an immunoassay is alpha-MSH,. . . between NEI and alpha]MSH, NEI
and CRF, or NGE and GRF. Such a confirmatory assay would be useful, for example, in assaying **tumor** cells, from a patient thought to be suffering from a **cancer** involving aberrant expression of alpha-MSH, CRF or GRF, to ascertain whether the **cancer** does in fact entail aberrant expression of one of those hormones or entails instead aberrant expression of NEI, NGE or some other. . .

DETAILED DESCRIPTION OF THE INVENTION
Mammalian **melanin**-concentrating hormone (MCH) has now been isolated from rat hypothalami by acid extraction and purified substantially by immunoaffinity chromatography using antiserum directed against salmon MCH,. . .
. . .

color of a mammal comprising
administering thereto an effective amount of such a MCH,
a method of suppressing the proliferation of skin **tumor**
cells in a mammal comprising administering thereto an
effective amount of such a MCH, and a method of
suppressing the secretion of ACTH. . .

. . .

through nucleic acid probe
hybridization analysis clones containing MCH-encoding
sequences. If the library is an expression library,
screening of the library with anti-MCH **antibodies** (alone
or together with anti-NEI or anti-NGE **antibodies**) may
also be used, alone or in conjunction with nucleic acid
probe hybridization probing, to identify or confirm the
presence of MCH-encoding or. . .

Throughout the purification, fractions are
monitored using an RIA based upon this rabbit anti-salmon
MCH **antibody**. Aliquots for assay are transferred into
glass tubes containing BSA (10 Al of 10 mg/ml) and dried
in a Savant Speed Vac.. . . is carried out using
chilled reagents and with tubes partially immersed in ice
water. On day one, 100 Al of buffer with **Antibody**
PBL #171 1/24,000 dilution (1/120,000 final dilution) is
added to glass tubes containing standard or test samples
or buffer only in a volume. . . to all tubes. The tubes are
vortexed and returned to the cold for approximately 24
hours. On day three, tracer bound to **antibody** is
precipitated with sheep anti]rabbit gamma globulins (100
Ali 1/40 dilution) and 0.5 ml of 10%(w/v) polyethylene
glycol (SIGMA, MW = 6,000 to. . .

. . .

supernatant removed, and the reaction stopped by
resuspending the beads in 20 volumes (200 mls) of 0.02 M
ethanolamine-Cl, pH 8 The **antibody**]Protein A beads
are then washed twice with 1 N HAc and equilibrated with
50 mM Na HEPES, 150 mM NaCl, pH 7*5e. . .

. . .

of the peptide for the
topical application, and, in this respect, could rely
upon data generated in connection with the use of MSH
(**melanin** stimulating hormone) antagonists for this
purpose.

CLMEN I. A cyclic mammalian hormone capable of
concentrating mammalian **melanin**, which is a peptide with
about 19 residues, or a physiologically acceptable salt
of said mammalian hormone.
2* A mammalian hormone in accordance. . . which, if
expressed, would yield a polypeptide with the amino acid
sequence of a cyclic mammalian hormone, which is capable
of concentrating mammalian **melanin** and is a peptide with
about 19 residues, or, if said hormone is C]terminally
amidated, said amino acid sequence with a Gly. . .

=> s antibod? same melanin
84196 ANTIBOD?
661070 SAME
391 SAMES
661322 SAME
(SAME OR SAMES)
2796 MELANIN

```
          190 MELANINS
         2854 MELANIN
                (MELANIN OR MELANINS)
L34         0 ANTIBOD? SAME MELANIN
                (ANTIBOD?(W)SAME(W)MELANIN)

=> s antibod? (S) melanin
        84196 ANTIBOD?
         2796 MELANIN
          190 MELANINS
         2854 MELANIN
                (MELANIN OR MELANINS)
L35       118 ANTIBOD? (S) MELANIN

=> d his

     (FILE 'HOME' ENTERED AT 14:05:56 ON 23 JAN 2006)

     FILE 'MEDLINE' ENTERED AT 14:06:37 ON 23 JAN 2006
L1         9970 S MELANIN
L2        61483 S MELANOMA
L3         2328 S L2 AND L1
L4       705098 S ANTIBOD?
L5          198 S L3 AND L4
L6            7 S ANTI (2W) MELANIN
L7            2 S L6 AND L2
L8            0 S L7 AND L4

     FILE 'CAPLUS' ENTERED AT 14:09:05 ON 23 JAN 2006
L9        11188 S MELANIN
L10      690010 S CANCER OR TUMOR OR NEOPLAS? OR MELANOMA?
L11        1762 S L9 (L) L10
L12      451938 S ANTIBOD?
L13          60 S L11 AND L12
L14         190 S L9 (L) L12
L15          59 S L14 AND L10
L16          53 S L14 AND L13
L17          45 S L16 NOT PY>2002
L18      413661 S IN VIVO
L19           3 S L18 AND L17
L20           4 S L17 AND LABEL?
L21          46 S 6D2
L22           2 S L21 AND L10
L23          14 S ANTI (2W) MELANIN
L24           7 S L23 AND ANTIBOD?
L25           3 S L24 AND L10

     FILE 'PCTFULL' ENTERED AT 14:16:40 ON 23 JAN 2006
L26           6 S ANTI (2W) MELANIN
L27           1 S L26 AND ANTIBOD?
L28           3 S L26 AND (CANCER? OR TUMOR? OR NEOPLAS?)
L29           1 S WO 199011295/PN
L30           1 S MELANIN AND L29
L31           1 S L30 AND ANTIBOD?
L32       93014 S CANCER? OR TUMOR? OR NEOPLAS?
L33           1 S L32 AND L31
L34           0 S ANTIBOD? SAME MELANIN
L35         118 S ANTIBOD? (S) MELANIN

=> s l32 and l35
L36         106 L32 AND L35

=> s melanin/ab
```

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           214 MELANIN/AB
             9 MELANINS/AB
L37        217 MELANIN/AB
                 ((MELANIN OR MELANINS)/AB)

=> s melanin/ti
           100 MELANIN/TI
             6 MELANINS/TI
L38        106 MELANIN/TI
                 ((MELANIN OR MELANINS)/TI)

=> s l38 or l37
L39        239 L38 OR L37

=> s l39 and l36
L40         12 L39 AND L36

=> d ibib 1-6

L40    ANSWER 1 OF 12    PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:        2004093518 PCTFULL  ED 20041110  EW 200445
TITLE (ENGLISH):         IMMUNOSTIMULATORY AGENTS IN BOTANICALS
TITLE (FRENCH):          AGENTS IMMUNOSTIMULATEURS PRESENTS DANS DES PRODUITS
                         PHYTOPHARMACEUTIQUES
INVENTOR(S):             PASCO, David S, 706 Oakhill Drive, Oxford, MS 38655, US
                         [US, US];
                         PUGH, Nirmal, D, 401 Thacker Loop, Oxford, MS 38655, US
                         [US, US];
                         KHAN, Ikhlas, A, Shelia Drive 65, Oxford, MS 38655, US
                         [US, US];
                         MORAES, Rita, 307 Deer Run, Oxford, MS 38655, US [US,
                         US]
PATENT ASSIGNEE(S):      THE UNIVERSITY OF MISSISSIPPI, 125 Old Chemistry,
                         University, MS 38677, US [US, US], for all designates
                         States except US;
                         PASCO, David S, 706 Oakhill Drive, Oxford, MS 38655, US
                         [US, US], for US only;
                         PUGH, Nirmal, D, 401 Thacker Loop, Oxford, MS 38655, US
                         [US, US], for US only;
                         KHAN, Ikhlas, A, Shelia Drive 65, Oxford, MS 38655, US
                         [US, US], for US only;
                         MORAES, Rita, 307 Deer Run, Oxford, MS 38655, US [US,
                         US], for US only
AGENT:                   WILSON, Mandy$, Stites & Harbison PLLC, 400 West Market
                         Street, Suite 1800, Louisville, KY 40202-3352$, US
LANGUAGE OF FILING:      English
LANGUAGE OF PUBL.:       English
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER              KIND     DATE
                         ---------------------------------
                         WO 2004093518         A2 20041104
DESIGNATED STATES
       W:                AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO
                         CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR
                         HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV
                         MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO
                         RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ
                         VC VN YU ZA ZM ZW
       RW (ARIPO):       BW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
       RW (EAPO):        AM AZ BY KG KZ MD RU TJ TM
       RW (EPO):         AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU
                         MC NL PL PT RO SE SI SK TR
```

RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2004-US11886 A 20040416
PRIORITY INFO.: US 2003-60/463,169 20030416
US 2004-60/538,676 20040123

L40 ANSWER 2 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2002008290 PCTFULL ED 20020814
TITLE (ENGLISH): DOG **MELANIN**-CONCENTRATING HORMONE RECEPTOR
TITLE (FRENCH): RECEPTEUR DE L'HORMONE CONCENTRANT LA MELANINE DU CHIEN
INVENTOR(S): TAN, Carina, P.
PATENT ASSIGNEE(S): MERCK &CO., INC.;
TAN, Carina, P.
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2002008290	A1	20020131

DESIGNATED STATES
W: CA JP US AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
APPLICATION INFO.: WO 2001-US22458 A 20010717
PRIORITY INFO.: US 2000-60/219,669 20000721

L40 ANSWER 3 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2001098464 PCTFULL ED 20020826
TITLE (ENGLISH): CONTINUOUS ADHERENT MELANOCYTE CELL LINE
TITLE (FRENCH): LIGNEE CELLULAIRE ADHERENTE CONTINUE DE MELANOCYTE
INVENTOR(S): ALEXANDER, Jeannine;
COX, William, I.
PATENT ASSIGNEE(S): AVENTIS PASTEUR LIMITED;
ALEXANDER, Jeannine;
COX, William, I.
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001098464	A2	20011227

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2001-US40540 A 20010418
PRIORITY INFO.: US 2000-60/213,613 20000622

L40 ANSWER 4 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2000010507 PCTFULL ED 20020515
TITLE (ENGLISH): USE OF **MELANIN** FOR INHIBITION OF ANGIOGENESIS AND MACULAR DEGENERATION
TITLE (FRENCH): UTILISATION DE MELANINE POUR INHIBER L'ANGIOGENESE ET LA DEGENERESCENCE MACULAIRE
INVENTOR(S): D'AMATO, Robert, J.
PATENT ASSIGNEE(S): THE CHILDREN'S MEDICAL CENTER CORPORATION;
D'AMATO, Robert, J.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE

WO 2000010507 A2 20000302

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE

APPLICATION INFO.: WO 1999-US19026 A 19990820
PRIORITY INFO.: US 1998-60/097,385 19980821

L40 ANSWER 5 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1999006074 PCTFULL ED 20020515
TITLE (ENGLISH): USE OF TEXAPHYRINS IN DETECTION OF **MELANIN** AND **MELANIN** METABOLITES OF MELANOTIC MELANOMA
TITLE (FRENCH): UTILISATION DE TEXAPHYRINES DANS LA DETECTION DE LA MELANINE ET DES METABOLITES DE LA MELANINE DU MELANOME MELANIQUE
INVENTOR(S): WOODBURN, Kathryn, W.;
YOUNG, Stuart, W.
PATENT ASSIGNEE(S): PHARMACYCLICS, INC.;
WOODBURN, Kathryn, W.;
YOUNG, Stuart, W.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9906074	A1	19990211

DESIGNATED STATES
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 1998-US15833 A 19980729
PRIORITY INFO.: US 1997-08/903,099 19970730

L40 ANSWER 6 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1998034602 PCTFULL ED 20020514
TITLE (ENGLISH): MEDIATION OF CYTOKINES BY **MELANIN**
TITLE (FRENCH): REGULATION DE LA PRODUCTION DE CYTOKINES PAR LA MELANINE
INVENTOR(S): MOHAGHEGHPOUR, Nahid
PATENT ASSIGNEE(S): BIOSOURCE TECHNOLOGIES, INC.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9834602	A2	19980813

DESIGNATED STATES
W: AU BG CA IL JP KR MX AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE

APPLICATION INFO.: WO 1998-US2971 A 19980210
PRIORITY INFO.: US 1997-8/798,846 19970212

=> d kwic 4

L40 ANSWER 4 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
TIEN USE OF **MELANIN** FOR INHIBITION OF ANGIOGENESIS AND MACULAR DEGENERATION
ABEN Compositions and methods of using **melanin**, or **melanin** -promoting compounds, for inhibiting angiogenesis to treat angiogenesis-dependent diseases, such as macular degeneration and **cancer**.
ABFR . . . de melanine permettant d'inhiber l'angiogenese afin de traiter les maladies dependantes de l'angiogenese telles que la degenerescence maculaire et le **cancer**.

DETD . . . ANGIOGENESIS AND MACULAR DEGENERATION

Technical Field

This application relates to an inhibitor of ancriogenesis useful for treating angiogenesis-related diseases, such as macular degeneration and angiogenesis-dependent **cancers**. The invention further relates to novel pharmaceutical compositions and methods for treating and curing macular degeneration, and other angiogenesis-dependent diseases.

Persistent, unregulated angiogenesis occurs in a multiplicity of disease states, **tumor** metastasis and abnormal growth by endothelial cells and supports the pathological damage seen in these conditions. The diverse pathological states created due. . .

One of the most frequent angiogenic diseases of childhood is the hemangioma. In most cases, the **tumors** are benign and regress without intervention. In more severe cases, the **tumors** progress to large cavernous and infiltrative forms and create clinical complications. Systemic forms of hemangiomas, the hemangiomatoses, have a high mortality rate.

. . .

damage found in hereditary

9

diseases such as Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia. This is an inherited disease characterized by multiple small angiomas, **tumors** of blood or lymph vessels. The angiomas are found in the skin and mucous membranes, often accompanied by epistaxis (nosebleeds) or gastrointestinal. . .

Angiogenesis is prominent in solid **tumor** formation and metastasis. Several lines of direct evidence now suggest that angiogenesis is essential for the growth and persistence of solid **tumors** and their metastases (Folkman, 1989; Hori et al., 1991; Kim et al., 1993; Millauer et al., 1994).

To stimulate angiogenesis, **tumors** upregulate their production of a variety of angiogenic factors, including the fibroblast growth factors (FGF and BFGF) (Kandel et al., 1991) and vascular endothelial cell growth factor/vascular

permeability factor (VEGF/VPF). However, many malignant **tumors** also
generate inhibitors of anglogenesis, including angiostatin and
thrombospondin (Chen et al., 1995; Good et al., 1990; O'Reilly et al.,
1994).

. . .

et al.,
1989). Several other endogenous inhibitors of angiogenesis have been-
identified, although not all are associated with the presence of a
tumor.

Melanin pigments play a critical role in the development of skin
cancers such as melanoma, which involves **tumor**
development from
transformed melanocytes. Light-skinned individuals with more
pheomelanin tend to have a higher incidence of melanoma than darker
skinned individuals, perhaps due. . .

. . .

melanomas. This teaches away the current
invention in which increased levels of melanin are disclosed to decrease
angiogenesis (blood vessel formation in **tumors**) and thus lead
to decreased
tumor size and formation.

. . .

for treating or for repressing macular
degeneration. Administration of melanin, or a melanin-promoting
compound to a human or animal with prevascularized metastasized
tumors
prevents the growth or expansion of those **tumors**.

The present invention also includes diagnostic methods and kits
for detection and measurement of **melanin**, or a **melanin**
-promoting
compound, in biological fluids and tissues, and for localization of
melanin,
or a **melanin**-promoting compound, in tissues. The diagnostic
method and
kit can be in any configuration well known to those of ordinary skill in
the
art. The present invention also includes **antibodies** specific
for the **melanin**,
or a **melanin**-promoting compound, and **antibodies** that
inhibit the binding of
antibodies specific for the **melanin**, or a
melanin-promoting compound.

The **antibodies** specific for **melanin**, or a
melanin-promoting compound, can
be used in diagnostic kits to detect the presence and quantity of
melanin, or a
melanin-promoting compound, which is diagnostic or prognostic
for the
occurrence or recurrence of **cancer** or other disease mediated
by
angiogenesis. **Antibodies** specific for **melanin**, or a
melanin-promoting
compound, may also be administered to a human or animal to passively
immunize the human or animal against **melanin**, or a
melanin-promoting
compound, thereby reducing angiogenic inhibition.

The present invention also relates to methods of using the
melanin, or a **melanin**-promoting compound, fragments,

and **antibodies** that
bind specifically to the inhibitor and its fragments, to diagnose endothelial
cell-related diseases and disorders.

. . .

that are
mediated by angiogenesis including, but not limited to macular degeneration, corneal diseases, rubeosis, neovascular glaucoma, diabetic retinopathy, retrolental fibroplasia, hemangioma, solid **tumors**, leukernia,
metastasis, telanglectasia psoriasis scleroderma, pyogenic granuloma,
- 10 -
myocardial anglogenesis, plaque neovascularization, corornay collaterals,
cerebral collaterals, arteriovenous malformations, ischernic limb angiogenesis, arthritis, diabetic. . .

It is another object of the present invention to provide a composition for treating or repressing the growth of a **cancer**.

It is an object of present invention to provide a method for detecting and quantifying the presence of an **antibody** specific for an
melanin, or a **melanin**-promoting compound, in a body fluid.

Still another object of the present invention is to provide a composition consisting of **antibodies** to **melanin**, or a **melanin**-promoting
compound, that are selective for specific regions of the **melanin**, or a
melanin-promoting compound, molecule.

It is another object of the present invention to provide a method for the detection or prognosis of **cancer**.

Still another object of the present invention is to provide a composition comprising melanin, or a melanin-promoting compound, linked to a cytotoxic agent for treating or repressing the growth of a **cancer**.

. . .

inhibiting
angiogenesis are melanin and melanin-promoting compounds. The inhibitor compounds of the invention are useful for treating angiogenesis-related diseases, particularly macular degeneration, and angiogenesis-dependent
cancers and **tumors**. The unexpected and surprising ability of melanin to
treat and cure anglogenesis-dependent diseases answers a long felt and unfulfilled need in the. . .

. . .

inhibiting activity include the chick CAM assay,
the mouse corneal assay, and the effect of administering isolated or synthesized proteins on implanted **tumors**. The chick CAM assay is
described by O'Reilly, et al. in Angiogenic Regulation of Metastatic Growth Cell, vol. 79 (2), October 21,. . .

Cancer means angiogenesis-dependent **cancers** and
tumors, i.e. **tumors** that
require for their growth (expansion in volume and/or mass) an increase in
the number and density of the blood vessels supplying. . .

Regression refers to the reduction of **tumor** mass and size.

. . .

melanin, or
a melanin-promoting compound, in body fluids and tissues for the purpose of diagnosis or prognosis of angiogenesis-mediated diseases such as **cancer**.

. . .

tissues. The
present invention also includes methods of treating or preventing angiogenic
diseases and processes including, but not limited to, macular degeneration
and **tumors** by stimulating the production of melanin, and/or by administering substantially purified melanin, or a melanin-associated compound, or a fusion protein containing the. . .

Passive **antibody** therapy using **antibodies** that
specifically bind
melanin can be employed to modulate endothelial-dependent processes such
as reproduction, development, and wound healing and tissue repair.

Antibodies specific for **melanin**, or a
melanin-promoting compound, are
made according to techniques and protocols well-known in the art. The
- 13 -
antibodies may be either polyclonal or monoclonal. The **antibodies** are
utilized in well-know immunoassay formats, such as competitive and non-competitive immunoassays, including ELISA, sandwich immunoassays and radioimmunoassays (RlAs), to determine the. . .

. . .

limited to,
ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of
prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis; angiogenesis-dependent **cancer**,
including, for example, solid **tumors**, blood born
tumors such as leukemias,
and **tumor** metastases; benign **tumors**, for example
hemangiomas, acoustic
neuromas, neurofibromas, trachomas, and pyogenic granulomas; rheumatoid arthritis; psoriasis; Osler-Webber Syndrome; myocardial angiogenesis; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma;
and. . .

. . .

cardiac muscle
especially following transplantation of a heart or heart tissue and after
bypass surgery, promotion of vascularization of solid and relatively avascular **tumors** for enhanced cytotoxin delivery, and enhancement of
blood flow to the nervous system, including but not limited to the cerebral
cortex and. . .

. . .

destruction of cells that bind melanin. These cells may
be found in many locations, including but not limited to, micrometastases
and primary **tumors**. Peptides linked to cytotoxic agents are infused in a

manner designed to maximize delivery to the desired location. For example,
ricin-linked high. . . antagonists may be co-applied
with stimulators of anglogenesis to increase vascularization of tissue. This
therapeutic regimen provides an effective means of destroying metastatic **cancer**.

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a melanin-
promoting compound, may be used in combination with other compositions
and procedures for the treatment of diseases. For example, a **tumor** may be
treated conventionally with surgery, radiation or chemotherapy combined
with melanin, and then another anti-angiogenic compound may be
subsequently administered to the patient to extend the dormancy of
micrometastases and to stabilize any residual primary **tumor**.

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the compound, the
polymers being implanted in the vicinity of where drug delivery is desired,
for example, at the site of a **tumor** or implanted so that the endostatin is
slowly released systemically. Osmotic minipumps may also be used to
provide controlled delivery of high. . . through cannulae to the site of interest, such as
directly into a metastatic growth or into the vascular supply to that **tumor**.

Kits for measurement of **melanin**, or a **melanin**
-promoting
compound, are also contemplated as part of the present invention. Antisera
that possess the highest titer and specificity and can detect the. . .
and non-competitive assays,
radioimmunoassay, bioluminescence and chemiluminescence assays,
fluorometric assays, sandwich assays, immunoradiometric assays, dot blots,
enzyme linked assays including ELISA, microtiter plates,
antibody coated
- 18 -
strips or dipsticks for rapid monitoring of urine or blood, and
immunocytochernistry. For each kit the range, sensitivity, precision,
reliability,. . .

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in the pigmented layer of the eye,
or choroid, compared to white patients. Additionally, black patients have a
reduced incidence of vascular **tumors** in the skin such as childhood
hemangiomas. However, there are other inherent racial differences between
white and black individuals besides pigmentation, and. . .

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Angiostatin induces and sustains dormancy of human primary
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Inhibition
of angiogenesis and **tumor** growth by a synthetic laminin
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Polverini, P. J.,
and Bouck, N.. . .

Nad. **Cancer** Inst. 87, 581
Weiter, et al., (1985) 99 Am. J. Ophthal 185.

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L40 ANSWER 4 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2000010507 PCTFULL ED 20020515
TITLE (ENGLISH): USE OF **MELANIN** FOR INHIBITION OF ANGIOGENESIS AND MACULAR DEGENERATION
TITLE (FRENCH): UTILISATION DE MELANINE POUR INHIBER L'ANGIOGENESE ET LA DEGENERESCENCE MACULAIRE
INVENTOR(S): D'AMATO, Robert, J.
PATENT ASSIGNEE(S): THE CHILDREN'S MEDICAL CENTER CORPORATION; D'AMATO, Robert, J.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2000010507	A2	20000302

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
APPLICATION INFO.: WO 1999-US19026 A 19990820
PRIORITY INFO.: US 1998-60/097,385 19980821
TIEN USE OF **MELANIN** FOR INHIBITION OF ANGIOGENESIS AND MACULAR DEGENERATION

ABEN Compositions and methods of using **melanin**, or **melanin** -promoting compounds, for inhibiting angiogenesis to treat angiogenesis-dependent diseases, such as macular degeneration and **cancer**.

ABFR . . . de melanine permettant d'inhiber l'angiogenese afin de traiter les maladies dependantes de l'angiogenese telles que la degenerescence maculaire et le **cancer**.

DETD . . . ANGIOGENESIS AND MACULAR DEGENERATION

Technical Field

This application relates to an inhibitor of ancriogenesis useful for treating angiogenesis-related diseases, such as macular degeneration and angiogenesis-dependent **cancers**. The invention further relates to novel pharmaceutical compositions and methods for treating and curing macular degeneration, and other angiogenesis-dependent diseases.

Persistent, unregulated angiogenesis occurs in a multiplicity of disease states, **tumor** metastasis and abnormal growth by endothelial cells and supports the pathological damage seen in these conditions. The diverse pathological states created due. . .

One of the most frequent angiogenic diseases of childhood is the hemangioma. In most cases, the **tumors** are benign and regress without intervention. In more severe cases, the **tumors** progress to large cavernous and infiltrative forms and create clinical complications. Systemic forms of hemangiomas, the hemangiomatoses, have a high mortality rate.

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damage found in hereditary

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diseases such as Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia. This is an inherited disease characterized by multiple small angiomas, **tumors** of blood or lymph vessels. The angiomas are found in the skin and mucous membranes, often accompanied by epistaxis (nosebleeds) or gastrointestinal. . .

Angiogenesis is prominent in solid **tumor** formation and metastasis. Several lines of direct evidence now suggest that angiogenesis is essential for the growth and persistence of solid **tumors** and their metastases (Folkman, 1989; Hori et al., 1991; Kim et al., 1993; Millauer et al., 1994).

To stimulate angiogenesis, **tumors** upregulate their production of a variety of angiogenic factors, including the fibroblast growth factors (FGF and BFGF) (Kandel et al., 1991) and vascular endothelial cell growth factor/vascular permeability factor (VEGF/VPF). However, many malignant **tumors** also generate inhibitors of anglogenesis, including angiostatin and

thrombospondin (Chen et al., 1995; Good et al., 1990; O'Reilly et al., 1994).

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et al., 1989). Several other endogenous inhibitors of angiogenesis have been-identified, although not all are associated with the presence of a **tumor**.

Melanin pigments play a critical role in the development of skin **cancers** such as melanoma, which involves **tumor** development from transformed melanocytes. Light-skinned individuals with more pheomelanin tend to have a higher incidence of melanoma than darker skinned individuals, perhaps due. . .

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melanomas. This teaches away the current invention in which increased levels of melanin are disclosed to decrease angiogenesis (blood vessel formation in **tumors**) and thus lead to decreased **tumor** size and formation.

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for treating or for repressing macular degeneration. Administration of melanin, or a melanin-promoting compound to a human or animal with prevascularized metastasized **tumors** prevents the growth or expansion of those **tumors**.

The present invention also includes diagnostic methods and kits for detection and measurement of **melanin**, or a **melanin**-promoting compound, in biological fluids and tissues, and for localization of **melanin**, or a **melanin**-promoting compound, in tissues. The diagnostic method and kit can be in any configuration well known to those of ordinary skill in the art. The present invention also includes **antibodies** specific for the **melanin**, or a **melanin**-promoting compound, and **antibodies** that inhibit the binding of **antibodies** specific for the **melanin**, or a **melanin**-promoting compound.

The **antibodies** specific for **melanin**, or a **melanin**-promoting compound, can be used in diagnostic kits to detect the presence and quantity of **melanin**, or a **melanin**-promoting compound, which is diagnostic or prognostic for the occurrence or recurrence of **cancer** or other disease mediated by angiogenesis. **Antibodies** specific for **melanin**, or a **melanin**-promoting compound, may also be administered to a human or animal to passively immunize the human or animal against **melanin**, or a **melanin**-promoting compound, thereby reducing angiogenic inhibition.

The present invention also relates to methods of using the **melanin**, or a **melanin**-promoting compound, fragments, and **antibodies** that bind specifically to the inhibitor and its fragments, to diagnose endothelial

cell-related diseases and disorders.

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that are
mediated by angiogenesis including, but not limited to macular degeneration, corneal diseases, rubeosis, neovascular glaucoma, diabetic retinopathy, retrolental fibroplasia, hemangioma, solid **tumors**
, leukernia,
metastasis, telanglectasia psoriasis scleroderma, pyogenic granuloma,
- 10 -
myocardial anglogenesis, plaque neovascularization, corornay
collaterals,
cerebral collaterals, arteriovenous malformations, ischernic limb angiogenesis, arthritis, diabetic. . .

It is another object of the present invention to provide a composition for treating or repressing the growth of a **cancer**.

It is an object of present invention to provide a method for detecting and quantifying the presence of an **antibody** specific for an
melanin, or a **melanin**-promoting compound, in a body fluid.

Still another object of the present invention is to provide a composition consisting of **antibodies** to **melanin**, or a **melanin**-promoting
compound, that are selective for specific regions of the **melanin**
, or a
melanin-promoting compound, molecule.

It is another object of the present invention to provide a method for the detection or prognosis of **cancer**.

Still another object of the present invention is to provide a composition comprising melanin, or a melanin-promoting compound, linked to a cytotoxic agent for treating or repressing the growth of a **cancer**.

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inhibiting
angiogenesis are melanin and melanin-promoting compounds. The inhibitor compounds of the invention are useful for treating angiogenesis-related diseases, particularly macular degeneration, and angiogenesis-dependent
cancers and **tumors**. The unexpected and surprising ability of melanin to
treat and cure anglogenesis-dependent diseases answers a long felt and unfulfilled need in the. . .

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inhibiting activity include the chick CAM assay,
the mouse corneal assay, and the effect of administering isolated or synthesized proteins on implanted **tumors**. The chick CAM assay is
described by O'Reilly, et al. in Angiogenic Regulation of Metastatic Growth Cell, vol. 79 (2), October 21,. . .

Cancer means angiogenesis-dependent **cancers** and
tumors, i.e. **tumors** that
require for their growth (expansion in volume and/or mass) an increase in
the number and density of the blood vessels supplying. . .

Regression refers to the reduction of **tumor** mass and size.

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melanin, or

a melanin-promoting compound, in body fluids and tissues for the purpose of diagnosis or prognosis of angiogenesis-mediated diseases such as **cancer**.

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tissues. The present invention also includes methods of treating or preventing angiogenic diseases and processes including, but not limited to, macular degeneration and **tumors** by stimulating the production of melanin, and/or by administering substantially purified melanin, or a melanin-associated compound, or a fusion protein containing the. . .

Passive **antibody** therapy using **antibodies** that specifically bind **melanin** can be employed to modulate endothelial-dependent processes such as reproduction, development, and wound healing and tissue repair.

Antibodies specific for **melanin**, or a **melanin**-promoting compound, are made according to techniques and protocols well-known in the art. The - 13 - **antibodies** may be either polyclonal or monoclonal. The **antibodies** are utilized in well-know immunoassay formats, such as competitive and non-competitive immunoassays, including ELISA, sandwich immunoassays and radioimmunoassays (RlAs), to determine the. . .

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limited to, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis; angiogenesis-dependent **cancer**, including, for example, solid **tumors**, blood born **tumors** such as leukemias, and **tumor** metastases; benign **tumors**, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; rheumatoid arthritis; psoriasis; Osler-Webber Syndrome; myocardial angiogenesis; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; and. . .

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cardiac muscle especially following transplantation of a heart or heart tissue and after bypass surgery, promotion of vascularization of solid and relatively avascular **tumors** for enhanced cytotoxin delivery, and enhancement of blood flow to the nervous system, including but not limited to the cerebral cortex and. . .

. . .

destruction of cells that bind melanin. These cells may be found in many locations, including but not limited to, micrometastases and primary **tumors**. Peptides linked to cytotoxic agents are infused in a manner designed to maximize delivery to the desired location. For example, ricin-linked high. . . antagonists may be co-applied

with stimulators of anglogenesis to increase vascularization of tissue. This
therapeutic regimen provides an effective means of destroying metastatic **cancer**.

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a melanin-
promoting compound, may be used in combination with other compositions and procedures for the treatment of diseases. For example, a **tumor** may be
treated conventionally with surgery, radiation or chemotherapy combined with melanin, and then another anti-angiogenic compound may be subsequently administered to the patient to extend the dormancy of micrometastases and to stabilize any residual primary **tumor**.

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the compound, the
polymers being implanted in the vicinity of where drug delivery is desired,
for example, at the site of a **tumor** or implanted so that the endostatin is
slowly released systemically. Osmotic minipumps may also be used to provide controlled delivery of high. . . through cannulae to the site of interest, such as
directly into a metastatic growth or into the vascular supply to that **tumor**.

Kits for measurement of **melanin**, or a **melanin**
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compound, are also contemplated as part of the present invention. Antisera
that possess the highest titer and specificity and can detect the. . . and non-competitive assays,
radioimmunoassay, bioluminescence and chemiluminescence assays, fluorometric assays, sandwich assays, immunoradiometric assays, dot blots,
enzyme linked assays including ELISA, microtiter plates, **antibody** coated
- 18 -
strips or dipsticks for rapid monitoring of urine or blood, and immunocytochernistry. For each kit the range, sensitivity, precision, reliability,. . .

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in the pigmented layer of the eye,
or choroid, compared to white patients. Additionally, black patients have a
reduced incidence of vascular **tumors** in the skin such as childhood
hemangiomas. However, there are other inherent racial differences between
white and black individuals besides pigmentation, and. . .

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Chen, C., Parangi, S., Tolentino, M. J., and Folkman, J. (1995). A strategy to
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Clapp, C., Martial, J. A., Guzman, R. C., Rentier-Delrue, F., and Weiner, R.

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inhibitor of angiogenesis is immunologically and functionally indistinguishable from a fragment of thrombospondin. Proc. Nat. Acad. Sci.
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Res. 51, 6180
Kandel, J., Bossy-Wetzel, E., Radvany, F., Klagsburn, M., Folkinan, J., and
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McFerran, N. V. (1995). Murine epidermal growth factor (EGF) fragment (33-42) inhibits both EGF- and laminin-dependent endothelial cell motility
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Flynn, E., Birkhead, J.R., Olsen, B.J., Folkman, J. (1997). Endostatin: An
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Pawlek et al., (1973) 46 Yale J. Bio-Med. 430.
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F., Polverini, P. J., and Bouck, N. P. (1989). Regulation of the activity of a new inhibitor of angiogenesis by a **cancer** suppressor gene. Cell
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Sakamato, N., Iwahana, M., Tanaka, N. G., and Osaka, 8. (1991). Inhibition
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Salorninski and Paus, (1994) 103 J. Invest. Derm. 742.

(1994). Potentiation of cytotoxic **cancer** therapies by TNP-470 alone and
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30 Tolsma, S. S., Volpert, 0. V., Good, D. J., Frazier, W. A., Polverini, P. J.,
and Bouck, N.. . .

Nad. **Cancer** Inst. 87, 581
Weiter, et al., (1985) 99 Am. J. Ophthal 185.

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L40 ANSWER 7 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1997000892 PCTFULL ED 20020514
TITLE (ENGLISH): DEPIGMENTING ACTIVITY OF AGOUTI SIGNAL PROTEIN AND PEPTIDES THEREOF
TITLE (FRENCH): ACTIVITE DE DEPIGMENTATION DE LA PROTEINE-SIGNAL D'AGOUTI ET SES PEPTIDES
INVENTOR(S): HEARING, Vincent, J., Jr.
PATENT ASSIGNEE(S): THE GOVERNMENT OF THE UNITED STATES OF AMERICA, represented by THE SECRETARY DEPARTMENT OF HEALTH AND HUMAN SERVICES;
HEARING, Vincent, J., Jr.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9700892	A2	19970109

DESIGNATED STATES
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
APPLICATION INFO.: WO 1996-US10695 A 19960621
PRIORITY INFO.: US 1995-60/000,436 19950623

L40 ANSWER 8 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1995009629 PCTFULL ED 20020514
TITLE (ENGLISH): SYNTHETIC **MELANIN**

TITLE (FRENCH): MELANINE SYNTHETIQUE
INVENTOR(S): PAWELEK, John, M.
PATENT ASSIGNEE(S): YALE UNIVERSITY
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9509629	A1	19950413

DESIGNATED STATES
W: AM AU BB BG BR BY CA CN CZ EE FI GE HU JP KE KG KR KZ LK LR LT LV MD MG MN MW NO NZ PL RO RU SD SI SK TJ TT UA UZ VN KE MW SD SZ AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
APPLICATION INFO.: WO 1994-US10835 A 19940926
PRIORITY INFO.: US 1993-131,270 19931001

L40 ANSWER 9 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1992018166 PCTFULL ED 20020513
TITLE (ENGLISH): **MELANIN**-BASED AGENTS FOR IMAGE ENHANCEMENT
TITLE (FRENCH): AGENTS A BASE DE MELANINE UTILISES POUR LE REHAUSSEMENT DES IMAGES
INVENTOR(S): WILLIAMS, Robert, F.
PATENT ASSIGNEE(S): BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM; WILLIAMS, Robert, F.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9218166	A1	19921029

DESIGNATED STATES
W: AT AU BB BE BF BG BJ BR CA CF CG CH CI CM CS DE DK ES FI FR GA GB GN GR HU IT JP KP KR LK LU MC MG ML MN MR MW NL NO PL RO RU SD SE SN TD TG US
APPLICATION INFO.: WO 1992-US3177 A 19920415
PRIORITY INFO.: US 1991-685,937 19910415

L40 ANSWER 10 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1992007580 PCTFULL ED 20020513
TITLE (ENGLISH): THERAPEUTIC USES OF **MELANIN**
TITLE (FRENCH): UTILISATIONS THERAPEUTIQUES DE LA MELANINE
INVENTOR(S): BERLINER, David, L.; ERWIN, Robert, L.; McGEE, David, R.
PATENT ASSIGNEE(S): BIOSOURCE GENETICS CORPORATION
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9207580	A1	19920514

DESIGNATED STATES
W: AT AU BE CA CH DE DK ES FI FR GB GR IT JP LU NL NO SE
APPLICATION INFO.: WO 1991-US8213 A 19911105
PRIORITY INFO.: US 1990-609,311 19901105

L40 ANSWER 11 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1990012869 PCTFULL ED 20020513
TITLE (ENGLISH): NON-MELANOCYTIC, EUCARYOTIC CELL CONSTITUTIVELY EXPRESSING BIOLOGICALLY ACTIVE HUMAN TYROSINASE AND USE THEREOF

TITLE (FRENCH): CELLULE EUCARYOTE NON MELANOCYTIQUE EXPRIMANT DE MANIERE CONSTITUTIVE LA TYROSINASE HUMAINE BIOLOGIQUEMENT ACTIVE, ET SON UTILISATION
INVENTOR(S): BOUCHARD, Brigitte;
HOUGTON, Alan, N.
PATENT ASSIGNEE(S): SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9012869	A1	19901101

DESIGNATED STATES
W: AT BE CA CH DE DK ES FR GB IT JP LU NL SE
APPLICATION INFO.: WO 1990-US2288 A 19900426
PRIORITY INFO.: US 1989-343,960 19890426

L40 ANSWER 12 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1990011295 PCTFULL ED 20020513
TITLE (ENGLISH): **MELANIN**-CONCENTRATING HORMONES AND METHODS OF TREATMENT USING SAME
TITLE (FRENCH): HORMONES CONCENTRANT LA MELANINE ET PROCEDES DE TRAITEMENT UTILISANT DE TELLES HORMONES
INVENTOR(S): VAUGHAN, Joan;
FISCHER, Wolfgang, Hermann;
RIVIER, Jean, Edouard;
NAHON, Jean-Louis, Marie;
PRESSE, Francoise, Genevieve;
VALE, Wylie, Walker, Jr.
PATENT ASSIGNEE(S): THE SALK INSTITUTE FOR BIOLOGICAL STUDIES
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9011295	A1	19901004

DESIGNATED STATES
W: AT BE CA CH DE DK ES FR GB IT JP LU NL SE
APPLICATION INFO.: WO 1990-US1492 A 19900320
PRIORITY INFO.: US 1989-326,984 19890322

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L40 ANSWER 8 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
TIEN SYNTHETIC **MELANIN**
ABEN A **melanin** that is soluble in an aqueous solution at a pH between 5 and 9 at a temperature of 0 to 100 °C. Advantageously, the **melanin** is capable of being filtered through at least a 0.45 micron size filter, and has a molecular weight of greater than 10,000 kilodaltons. The **melanin** is useful for providing a naturally-appearing tan to mammalian skin and hair. Such **melanin** can be produced by combining dopachrome and an appropriate enzyme, or by incubating 5,6-dihydroxyindole-2-carboxylic acid alone or with 5,6-dihydroxyindole, or with 3-amino-tyrosine. The **melanin** is also useful for providing a sun-screen to mammalian skin and hair, to treat post-inflammatory hypo- and hyperpigmentation, to tint. . . as a coloring agent in foodstuffs such as coffee, tea, soda, whisky and liquors. Also included are self-tanning compositions containing **melanin** and

DHA.

DETD . . . which absorb ultraviolet radiation and, thus, provide protection from its harmful effects, such as premature skin aging and the occurrence of skin **cancers**.

tyrosinase: Ann Korner and John Pawelek, Mammalian Tyrosinase Catalyzes Three Reactions in the Biosynthesis of 5 **Melanin**. Science, 217:1163-1165, 1982; dopachrome tautomerase: John Pawelek, After Dopachrome?, Pigment Cell Research, 4:53-62, 1991, glycoprotein 75: Timothy M. Thomson, M. Jules Mattes, Linda Roux, Lloyd Old and Kenneth 0, Lloyd, io Pigmentation-associated Glycoprotein of Human Melanomas and Melanocytes: Definition with a Mouse Monoclonal **Antibody**, J, Invest. Derm,, 85:169-174, 1985; MSH receptor: Seth J. Orlow, Sara Hotchkiss, and John M. Pawelek, Internal Binding Sites for MSH: Analyses in Wild Type and Variant Cloudman Melanoma Cells,, J, Cellular Physiology,, 142:129 136, 1990, The **melanins** according to the present invention can be admixed with a physiologically acceptable carrier to form a composition, which has the uses previously. . .

=> s wo2000010507/pn
L41 1 WO2000010507/PN
(WO2000010507/PN)

=> s l41 and label?
131550 LABEL?
L42 1 L41 AND LABEL?

=> d kwic

L42 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2006 Univentio on STN
PI **WO 2000010507** **A2 20000302**

DETD The present invention also includes melanin, or a melanin-promoting compound, that can be **labeled** isotopically or with other molecules or proteins for use in the detection and visualization of melanin, or a melanin-promoting compound, sites with. . .
. . .
Sci. USA 76,
5217
Gavrieli, Y., Sherman, Y., and Ben-Sasson, S. A. (1992). Identification of programmed cell death in situ via specific **labeling** of nuclear DNA fragmentation. J. Cell Biol.. 119, 493
Good, D. J., Polverini, P. J., Rastinejad, F., Le Beau, M. M.,. . .

ACCESSION NUMBER: 2000010507 PCTFULL ED 20020515
TITLE (ENGLISH): USE OF **MELANIN** FOR INHIBITION OF ANGIOGENESIS AND MACULAR DEGENERATION
TITLE (FRENCH): UTILISATION DE MELANINE POUR INHIBER L'ANGIOGENESE ET LA DEGENERESCENCE MACULAIRE
INVENTOR(S): D'AMATO, Robert, J.
PATENT ASSIGNEE(S): THE CHILDREN'S MEDICAL CENTER CORPORATION; D'AMATO, Robert, J.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000010507	A2	20000302

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
APPLICATION INFO.: WO 1999-US19026 A 19990820
PRIORITY INFO.: US 1998-60/097,385 19980821

TIEN USE OF **MELANIN** FOR INHIBITION OF ANGIOGENESIS AND MACULAR DEGENERATION

ABEN Compositions and methods of using **melanin**, or **melanin**-promoting compounds, for inhibiting angiogenesis to treat angiogenesis-dependent diseases, such as macular degeneration and **cancer**.

ABFR . . . de melanine permettant d'inhiber l'angiogenese afin de traiter les maladies dependantes de l'angiogenese telles que la degenerescence maculaire et le **cancer**.

DETD . . . ANGIOGENESIS AND MACULAR DEGENERATION

Technical Field

This application relates to an inhibitor of ancriogenesis useful for treating angiogenesis-related diseases, such as macular degeneration and angiogenesis-dependent **cancers**. The invention further relates to novel pharmaceutical compositions and methods for treating and curing macular degeneration, and other angiogenesis-dependent diseases.

Persistent, unregulated angiogenesis occurs in a multiplicity of disease states, **tumor** metastasis and abnormal growth by endothelial cells and supports the pathological damage seen in these conditions. The diverse pathological states created due. . .

One of the most frequent angiogenic diseases of childhood is the hemangioma. In most cases, the **tumors** are benign and regress without intervention. In more severe cases, the **tumors** progress to large cavernous and infiltrative forms and create clinical complications. Systemic forms of hemangiomas, the hemangiomatoses, have a high mortality rate.

. . . damage found in hereditary

diseases such as Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia. This is an inherited disease characterized by multiple small angiomas, **tumors** of blood or lymph vessels. The angiomas are found in the skin and mucous membranes, often accompanied by epistaxis (nosebleeds) or gastrointestinal. . .

Angiogenesis is prominent in solid **tumor** formation and metastasis. Several lines of direct evidence now suggest that angiogenesis is essential for the growth and persistence of solid **tumors** and their metastases (Folkman, 1989; Hori et al., 1991; Kim et al., 1993; Millauer et al., 1994).

To stimulate angiogenesis, **tumors** upregulate their production of a variety of angiogenic factors, including the fibroblast growth factors (FGF and BFGF) (Kandel et al., 1991) and vascular endothelial cell growth factor/vascular permeability factor (VEGF/VPF). However, many malignant **tumors** also generate inhibitors of anglogenesis, including angiostatin and thrombospondin (Chen et al., 1995; Good et al., 1990; O'Reilly et al., 1994).

. . . et al., 1989). Several other endogenous inhibitors of angiogenesis have been-identified, although not all are associated with the presence of a **tumor**.

Melanin pigments play a critical role in the development of skin **cancers** such as melanoma, which involves **tumor** development from transformed melanocytes. Light-skinned individuals with more pheomelanin tend to have a higher incidence of melanoma than darker skinned individuals, perhaps due. . .

. . . melanomas. This teaches away the current invention in which increased levels of melanin are disclosed to decrease angiogenesis (blood vessel formation in **tumors**) and thus lead to decreased **tumor** size and formation.

. . . for treating or for repressing macular degeneration. Administration of melanin, or a melanin-promoting compound to a human or animal with prevascularized metastasized **tumors** prevents the growth or expansion of those **tumors**.

The present invention also includes diagnostic methods and kits for detection and measurement of **melanin**, or a **melanin**-promoting compound, in biological fluids and tissues, and for localization of **melanin**, or a **melanin**-promoting compound, in tissues. The diagnostic method and kit can be in any configuration well known to those of ordinary skill in the art. The present invention also includes **antibodies** specific

for the **melanin**,
or a **melanin**-promoting compound, and **antibodies** that
inhibit the binding of
antibodies specific for the **melanin**, or a
melanin-promoting compound.

The **antibodies** specific for **melanin**, or a
melanin-promoting compound, can
be used in diagnostic kits to detect the presence and quantity of
melanin, or a
melanin-promoting compound, which is diagnostic or prognostic
for the
occurrence or recurrence of **cancer** or other disease mediated
by
angiogenesis. **Antibodies** specific for **melanin**, or a
melanin-promoting
compound, may also be administered to a human or animal to passively
immunize the human or animal against **melanin**, or a
melanin-promoting
compound, thereby reducing angiogenic inhibition.

The present invention also relates to methods of using the
melanin, or a **melanin**-promoting compound, fragments,
and **antibodies** that
bind specifically to the inhibitor and its fragments, to diagnose
endothelial
cell-related diseases and disorders.

. . .
that are
mediated by angiogenesis including, but not limited to macular
degeneration, corneal diseases, rubeosis, neovascular glaucoma, diabetic
retinopathy, retrolental fibroplasia, hemangioma, solid **tumors**
, leukernia,
metastasis, telanglectasia psoriasis scleroderma, pyogenic granuloma,
- 10 -
myocardial anglogenesis, plaque neovascularization, corornay
collaterals,
cerebral collaterals, arteriovenous malformations, ischernic limb
angiogenesis, arthritis, diabetic. . .

It is another object of the present invention to provide a
composition for treating or repressing the growth of a **cancer**.

It is an object of present invention to provide a method for
detecting and quantifying the presence of an **antibody** specific
for an
melanin, or a **melanin**-promoting compound, in a body
fluid.

Still another object of the present invention is to provide a
composition consisting of **antibodies** to **melanin**, or
a **melanin**-promoting
compound, that are selective for specific regions of the **melanin**
, or a
melanin-promoting compound, molecule.

It is another object of the present invention to provide a method
for the detection or prognosis of **cancer**.

Still another object of the present invention is to provide a
composition comprising melanin, or a melanin-promoting compound, linked
to a cytotoxic agent for treating or repressing the growth of a
cancer.

. . .
inhibiting
angiogenesis are melanin and melanin-promoting compounds. The inhibitor compounds of the invention are useful for treating angiogenesis-related diseases, particularly macular degeneration, and angiogenesis-dependent **cancers** and **tumors**. The unexpected and surprising
ability of melanin to
treat and cure anglogenesis-dependent diseases answers a long felt and unfulfilled need in the. . .
. . .
inhibiting activity include the chick CAM assay,
the mouse corneal assay, and the effect of administering isolated or synthesized proteins on implanted **tumors**. The chick CAM assay
is
described by O'Reilly, et al. in Angiogenic Regulation of Metastatic Growth Cell, vol. 79 (2), October 21,. . .

Cancer means angiogenesis-dependent **cancers** and
tumors, i.e. **tumors** that
require for their growth (expansion in volume and/or mass) an increase
in
the number and density of the blood vessels supplying. . .

Regression refers to the reduction of **tumor** mass and size.
. . .
melanin, or
a melanin-promoting compound, in body fluids and tissues for the purpose of diagnosis or prognosis of angiogenesis-mediated diseases such as **cancer**.
. . .
tissues. The
present invention also includes methods of treating or preventing
angiogenic
diseases and processes including, but not limited to, macular
degeneration
and **tumors** by stimulating the production of melanin, and/or by administering substantially purified melanin, or a melanin-associated compound, or a fusion protein containing the. . .

Passive **antibody** therapy using **antibodies** that
specifically bind
melanin can be employed to modulate endothelial-dependent
processes such
as reproduction, development, and wound healing and tissue repair.

Antibodies specific for **melanin**, or a
melanin-promoting compound, are
made according to techniques and protocols well-known in the art. The
- 13 -
antibodies may be either polyclonal or monoclonal. The
antibodies are
utilized in well-know immunoassay formats, such as competitive and non-competitive immunoassays, including ELISA, sandwich immunoassays and radioimmunoassays (RlAs), to determine the. . .
. . .
limited to,
ocular angiogenic diseases, for example, diabetic retinopathy,
retinopathy of
prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis; angiogenesis-dependent
cancer,
including, for example, solid **tumors**, blood born
tumors such as leukemias,

and **tumor** metastases; benign **tumors**, for example
hemangiomas, acoustic
neuromas, neurofibromas, trachomas, and pyogenic granulomas; rheumatoid
arthritis; psoriasis; Osler-Webber Syndrome; myocardial angiogenesis;
plaque neovascularization; telangiectasia; hemophiliac joints;
angiofibroma;
and. . .
. . .
cardiac muscle
especially following transplantation of a heart or heart tissue and
after
bypass surgery, promotion of vascularization of solid and relatively
avascular **tumors** for enhanced cytotoxin delivery, and
enhancement of
blood flow to the nervous system, including but not limited to the
cerebral
cortex and. . .
. . .
destruction of cells that bind melanin. These cells may
be found in many locations, including but not limited to,
micrometastases
and primary **tumors**. Peptides linked to cytotoxic agents are
infused in a
manner designed to maximize delivery to the desired location. For
example,
ricin-linked high. . . antagonists may be co-applied
with stimulators of anglogenesis to increase vascularization of tissue.
This
therapeutic regimen provides an effective means of destroying metastatic
cancer.
. . .
a melanin-
promoting compound, may be used in combination with other compositions
and procedures for the treatment of diseases. For example, a
tumor may be
treated conventionally with surgery, radiation or chemotherapy combined
with melanin, and then another anti-angiogenic compound may be
subsequently administered to the patient to extend the dormancy of
micrometastases and to stabilize any residual primary **tumor**.
. . .
the compound, the
polymers being implanted in the vicinity of where drug delivery is
desired,
for example, at the site of a **tumor** or implanted so that the
endostatin is
slowly released systemically. Osmotic minipumps may also be used to
provide controlled delivery of high. . . through cannulae to the site
of interest, such as
directly into a metastatic growth or into the vascular supply to that
tumor.

Kits for measurement of **melanin**, or a **melanin**
-promoting
compound, are also contemplated as part of the present invention.
Antisera
that possess the highest titer and specificity and can detect the. . .
and non-competitive assays,
radioimmunoassay, bioluminescence and chemiluminescence assays,
fluorometric assays, sandwich assays, immunoradiometric assays, dot
blots,
enzyme linked assays including ELISA, microtiter plates,
antibody coated

strips or dipsticks for rapid monitoring of urine or blood, and immunocytochernistry. For each kit the range, sensitivity, precision, reliability,. . .

. . .

in the pigmented layer of the eye,
or choroid, compared to white patients. Additionally, black patients have a
reduced incidence of vascular **tumors** in the skin such as childhood
hemangiomas. However, there are other inherent racial differences between
white and black individuals besides pigmentation, and. . .

. . .

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NEWS 10	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC
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NEWS 12	JAN 17	IPC 8 in the WPI family of databases including WPIFV

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```
=> s melanin
           261 MELANIN
            20 MELANINS
L1         267 MELANIN
                 (MELANIN OR MELANINS)

=> s 6D2
L2           1 6D2

=> s l2 and l1
L3           1 L2 AND L1

=> d ibib 1

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AUTHOR:             Garcia Rivera, Javier [Ph.D.]; Casadevall, Arturo [advisor]
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 NEWS  9  JAN 13   IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
 NEWS 10  JAN 13   New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to
                   INPADOC
 NEWS 11  JAN 17   Pre-1988 INPI data added to MARPAT
 NEWS 12  JAN 17   IPC 8 in the WPI family of databases including WPIFV
 NEWS 13  JAN 30   Saved answer limit increased
 NEWS 14  JAN 31   Monthly current-awareness alert (SDI) frequency
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=> s antibod?
L3 84196 ANTIBOD?

=> s l3/ti
L4 4045 (ANTIBOD?/TI)

=> s l4 and l2
L5 12 L4 AND L2

=> d ibib 1-6

L5 ANSWER 1 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2004069140 PCTFULL ED 20040825 EW 200434
TITLE (ENGLISH): ANTIGEN IMITATING EXTRACELLULAR AREAS OF MEMBRANE PROTEINS OF TYPE III PRODUCED FROM **INTRACELLULAR** PATHOGENIC MICRO-ORGANISMS, DERIVED CONFORMATIONAL **ANTIBODIES** AND THE USE THEREOF
TITLE (FRENCH): ANTIGENES MIMANT LES DOMAINES EXTRACELLULAIRES DE PROTEINES MEMBRANAIRES DE TYPE III ISSUES DE MICROORGANISMES INTRACELLULAIRES PATHOGENES, ANTICORPS CONFORMATIONNELS DERIVES ET LEURS APPLICATIONS
INVENTOR(S): TRANCHAND-BUNEL, Denis, 2, rue Jacques Brel, F-59790 Ronchin, FR [FR, FR]
PATENT ASSIGNEE(S): CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE, 3, rue Michel-Ange, F-75016 Paris, FR [FR, FR], for all designates States except US;
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TRANCHAND-BUNEL, Denis, 2, rue Jacques Brel, F-59790 Ronchin, FR [FR, FR], for US only
AGENT: CABINET ORES$, 36, rue de St Petersbourg, F-75008 Paris$, FR
LANGUAGE OF FILING: French
LANGUAGE OF PUBL.: French
DOCUMENT TYPE: Patent

PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2004069140	A2	20040819

DESIGNATED STATES

W:	AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
RW (ARIPO):	BW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
RW (EAPO):	AM AZ BY KG KZ MD RU TJ TM
RW (EPO):	AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
RW (OAPI):	BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.:	WO 2004-FR190 A 20040128
PRIORITY INFO.:	FR 2003-03/00943 20030128

L5 ANSWER 2 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN

ACCESSION NUMBER: 2004046192 PCTFULL ED 20040608 EW 200423

TITLE (ENGLISH): METHOD FOR ISOLATING **INTRACELLULAR ANTIBODIES** ABLE TO NEUTRALIZE PROTEIN INTERACTIONS

TITLE (FRENCH): METHODE D'ISOLEMENT D'ANTICORPS INTRACELLULAIRES VISANT A NEUTRALISER DES INTERACTIONS PROTEIQUES

INVENTOR(S): VISINTIN, Michela, c/o Lay Line Genomics S.P.A., Via di Castel Romano, 100, I-00128 Roma, IT [IT, IT];
CATTANEO, Antonino, c/o Lay Line Genomics S.p.A., Via di Castel Romano, 100, I-00128 Roma, IT [IT, IT]

PATENT ASSIGNEE(S): LAY LINE GENOMICS S.P.A., Via di Castel Romano, 100, I-00128 Roma, IT [IT, IT], for all designates States except US;
VISINTIN, Michela, c/o Lay Line Genomics S.P.A., Via di Castel Romano, 100, I-00128 Roma, IT [IT, IT], for US only;
CATTANEO, Antonino, c/o Lay Line Genomics S.p.A., Via di Castel Romano, 100, I-00128 Roma, IT [IT, IT], for US only

AGENT: CAPASSO, Olga$, De Simone & Partners S.p.A., Via V. Bellini, 20, I-00198 Roma$, IT

LANGUAGE OF FILING: English

LANGUAGE OF PUBL.: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2004046192	A2	20040603

DESIGNATED STATES

W:	AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
RW (ARIPO):	BW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
RW (EAPO):	AM AZ BY KG KZ MD RU TJ TM
RW (EPO):	AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
RW (OAPI):	BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.:	WO 2003-IT764 A 20031121
PRIORITY INFO.:	IT 2002-RM2002A000588 20021121

L5 ANSWER 3 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2004046185 PCTFULL ED 20040608 EW 200423
TITLE (ENGLISH): **INTRACELLULAR ANTIBODIES**
TITLE (FRENCH): ANTICORPS INTRACELLULAIRES
INVENTOR(S): RABBITTS, Terence, Howard, MRC Laboratory of Molecular Biology, Division Of Protein and Nucleic Acid Chemistry, Hills Road, Cambridge CB2 2QH, GB [GB, GB]; TANAKA, Tomoyuki, MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, GB [JP, GB]
PATENT ASSIGNEE(S): MEDICAL RESEARCH COUNCIL, 20 Park Crescent, London W1B 1AL, GB [GB, GB], for all designates States except US; RABBITTS, Terence, Howard, MRC Laboratory of Molecular Biology, Division Of Protein and Nucleic Acid Chemistry, Hills Road, Cambridge CB2 2QH, GB [GB, GB], for US only; TANAKA, Tomoyuki, MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, GB [JP, GB], for US only
AGENT: SAOMES, Candida$, D Young & Co, 21 New Fetter Lane, London EC4A 1DA$, GB
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004046185	A2	20040603

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
RW (ARIPO): BW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2003-GB4942 A 20031114
PRIORITY INFO.: GB 2002-0226729.2 20021115

L5 ANSWER 4 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2004030610 PCTFULL ED 20040421 EW 200416
TITLE (ENGLISH): COMPOSITIONS AND METHODS FOR THE **INTRACELLULAR** DELIVERY OF **ANTIBODIES**
TITLE (FRENCH): COMPOSITIONS ET PROCEDES POUR LA DELIVRANCE INTRACELLULAIRE D'ANTICORPS
INVENTOR(S): ERLANGER, Bernard, 163-16 15 Drive, Whitestone, NY 11357, US; CHEN, Bi-Xing, 1581 West Street, Fort Lee, NJ 07024, US
PATENT ASSIGNEE(S): THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK, West 116th Street & Broadway, New York, NY 10027, US [US, US]
AGENT: WHITE, John, P.$, Cooper & Dunham LLP, 1185 Avenue of the Americas, New York, NY 10036$, US
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004030610	A2	20040415

DESIGNATED STATES

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW

RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW

RW (EAPO): AM AZ BY KG KZ MD RU TJ TM

RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR

RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2003-US21842 A 20030711

PRIORITY INFO.: US 2002-60/395,363 20020711
US 2003-60/471,113 20030516

L5 ANSWER 5 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN

ACCESSION NUMBER: 2004011500 PCTFULL ED 20040211 EW 200406

TITLE (ENGLISH): SPECIFIC ISOTYPE **ANTIBODIES** OF SECRETION-EXCRETION ANTI-ANTIGENS OF <I>LEISHMANIA SP</I> OF PROMASTIGOTE<I> </I>OR AMASTIGOTE FORMS USED AS PROTECTION, RESISTANCE AND CURING MARKERS OF MAMMALS TO LEISHMANIASES AND TO **INTRACELLULAR** PATHOGENIC MICRO-ORGANISM INFECTIONS, AND AS IMMUNOTHERAPEUTIC EFFECTORS

TITLE (FRENCH): ANTICORPS D'ISOTYPES PARTICULIERS ANTI ANTIGENES D'EXCRETION SECRETION DE PROMASTIGOTES OU D'AMASTIGOTES DE LEISHMANIS SP UTILISES COMME MARQUEURS DE LA PROTECTION, DE LA RESISTANCE ET DE LA GUERISON DES MAMMIFERES AUX LEISHMANIOSES ET AUX INFECTIONS A MIRO-ORGANISMES PATHOGENES INTRACELLULAIRES, ET CO

INVENTOR(S): PAPIEROK, Gerard, Residence Reine Victoria, 38, avenue Riondet, F-83400 Hyeres, FR [FR, FR];
VICENS, Serge, 15, allee du Collet de Lebre, F-13180 Gignac la Nerthe, FR [FR, FR];
LEMESRE, Jean-Loup, 138, rue de Lodeve, Bat. 6 - D1, Residence Beau soleil, F-34000 Montpellier, FR [FR, FR]

PATENT ASSIGNEE(S): BIO VETO TESTS, BVT (SARL), 285, avenue de Rome - Parc d'Activite Les Playes, Jean Monnet Sud, F-83500 La Seyne sur Mer, FR [FR, FR], for all designates States except US;
PAPIEROK, Gerard, Residence Reine Victoria, 38, avenue Riondet, F-83400 Hyeres, FR [FR, FR], for US only;
VICENS, Serge, 15, allee du Collet de Lebre, F-13180 Gignac la Nerthe, FR [FR, FR], for US only;
LEMESRE, Jean-Loup, 138, rue de Lodeve, Bat. 6 - D1, Residence Beau soleil, F-34000 Montpellier, FR [FR, FR], for US only

AGENT: MAREK, Pierre$, 28 et 32, rue de la Loge, F-13002 Marseille$, FR

LANGUAGE OF FILING: French

LANGUAGE OF PUBL.: French

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004011500	A2	20040205

DESIGNATED STATES

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2003-FR2358 A 20030725
PRIORITY INFO.: FR 2002-02/09506 20020726

L5 ANSWER 6 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2003077945 PCTFULL ED 20031001 EW 200339
TITLE (ENGLISH): **INTRACELLULAR ANTIBODIES**
TITLE (FRENCH): ANTICORPS INTRACELLULAIRES
INVENTOR(S): LOBATO-CABALLERO, Maria, Natividad, MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, GB [ES, GB];
RABBITTS, Terence, Howard, MRC Laboratory of Molecular Biology, Division of Protein and Nucleic Acid Chemistry, Hills Road, Cambridge CB2 2QH, GB [GB, GB]
PATENT ASSIGNEE(S): MEDICAL RESEARCH COUNCIL, 20 Park Crescent, London W1B 1AL, GB [GB, GB], for all designates States except US;
LOBATO-CABALLERO, Maria, Natividad, MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, GB [ES, GB], for US only;
RABBITTS, Terence, Howard, MRC Laboratory of Molecular Biology, Division of Protein and Nucleic Acid Chemistry, Hills Road, Cambridge CB2 2QH, GB [GB, GB], for US only
AGENT: MASCHIO, Antonio$, D Young & Co., 21 New Fetter Lane, London EC4A 1DA$, GB
LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2003077945	A1	20030925

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
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RW (EAPO): AM AZ BY KG KZ MD RU TJ TM
RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2003-GB1077 A 20030314
PRIORITY INFO.: GB 2002-0206043.2 20020314
GB 2002-0226723.5 20021115
GB 2002-0226727.6 20021115

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(FILE 'HOME' ENTERED AT 15:06:49 ON 06 FEB 2006)

FILE 'PCTFULL' ENTERED AT 15:07:01 ON 06 FEB 2006
L1 41297 S INTRACELLULAR
L2 276 S L1/TI
L3 84196 S ANTIBOD?
L4 4045 S L3/TI
L5 12 S L4 AND L2

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=> s l5 and (?melanin)
          2853 ?MELANIN
L6           0 L5 AND (?MELANIN)

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L5 ANSWER 7 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN

ACCESSION NUMBER: 2003014960 PCTFULL ED 20030303 EW 200308

TITLE (ENGLISH): **INTRACELLULAR ANTIBODIES**

TITLE (FRENCH): ANTICORPS INTRACELLULAIRES

INVENTOR(S): CATTANEO, Antonio, International School of Advanced Studies (SISSA), Biophysic Sector, Via Beirut, 2/4, I-34014 Trieste, IT [IT, IT];
MARITAN, Amos, SISSA (Scuola Superiore Internazionale di Studi Av, anzati), Via Beirut 2-4, I-34014 Trieste, IT [IT, IT];
VISINTIN, Michela, SISSA (Scuola Superiore Internazionale di Studi Av, anzati), Via Beirut 2-4, I-34014 Trieste, IT [IT, IT];
RABBITTS, Terrence, Howard, Division of Protein and Nucleic Acid Chemistry, MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2HQ, GB [GB, GB];
SETTANNI, Giovanni, Strada Torino 12/A, I-10043 Orbassano, TO, IT [IT, IT]

PATENT ASSIGNEE(S): MEDICAL RESEARCH COUNCIL, 20 Park Crescent, London W1B 4AL, GB [GB, GB], for all designates States except US;
SISSA (SCUOLA SUPERIORE INTERNAZIONALE DI STUDI AVANZATI), Via Beirut 2-4, I-34014 Trieste, IT [IT, IT], for all designates States except US;
CATTANEO, Antonio, International School of Advanced Studies (SISSA), Biophysic Sector, Via Beirut, 2/4, I-34014 Trieste, IT [IT, IT], for US only;
MARITAN, Amos, SISSA (Scuola Superiore Internazionale di Studi Av, anzati), Via Beirut 2-4, I-34014 Trieste, IT [IT, IT], for US only;
VISINTIN, Michela, SISSA (Scuola Superiore Internazionale di Studi Av, anzati), Via Beirut 2-4, I-34014 Trieste, IT [IT, IT], for US only;
RABBITTS, Terrence, Howard, Division of Protein and Nucleic Acid Chemistry, MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2HQ, GB [GB, GB], for US only;
SETTANNI, Giovanni, Strada Torino 12/A, I-10043 Orbassano, TO, IT [IT, IT], for US only

AGENT: MASCHIO, Antonio$, D Young & Co, 21 New Fetter Lane, London EC4A 1DA$, GB

LANGUAGE OF FILING: English

LANGUAGE OF PUBL.: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2003014960	A2	20030220

DESIGNATED STATES

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

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RW (EAPO): AM AZ BY KG KZ MD RU TJ TM

RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LU MC

NL PT SE SK TR
RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2002-GB3512 A 20020801
PRIORITY INFO.: GB 2001-0119004.0 20010803
GB 2001-0121577.1 20010906
IT 2001-RM2001A000633 20011025
GB 2002-0200928.0 20020116
GB 2002-0203569.9 20020214

L5 ANSWER 8 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2000002922 PCTFULL ED 20020515
TITLE (ENGLISH): **ANTIBODY** AGAINST PROTEIN TYROSINE PHOSPHATASE **INTRACELLULAR** DOMAINS
TITLE (FRENCH): ANTICORPS SPECIFIQUE DES DOMAINES INTRACELLULAIRES DE LA THYROSINEPHOSPHATASE
INVENTOR(S): YAMAMOTO, Hiroshi;
TSUJIKAWA, Kazutake;
UCHINO, Yukiko
PATENT ASSIGNEE(S): FUSO PHARMACEUTICAL INDUSTRIES, LTD.;
YAMAMOTO, Hiroshi;
TSUJIKAWA, Kazutake;
UCHINO, Yukiko
LANGUAGE OF PUBL.: Japanese
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000002922	A1	20000120

DESIGNATED STATES
W: AU CA JP KR US AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
APPLICATION INFO.: WO 1999-JP3656 A 19990706
PRIORITY INFO.: JP 1998-PCT/JP98/03120 19980710

L5 ANSWER 9 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1998018489 PCTFULL ED 20020514
TITLE (ENGLISH): ENHANCEMENT OF TUMOR CELL CHEMOSENSITIVITY AND RADIOSENSITIVITY USING SINGLE CHAIN **INTRACELLULAR ANTIBODIES**
TITLE (FRENCH): AUGMENTATION DE LA CHIMIOSENSIBILITE ET DE LA RADIOSENSIBILITE DE CELLULES TUMORALES AU MOYEN D'ANTICORPS INTRACELLULAIRES A UNE SEULE CHAINE
INVENTOR(S): BUCHSBAUM, Donald, J.;
CURIEL, David, T.;
STACKHOUSE, Murray
PATENT ASSIGNEE(S): THE UAB RESEARCH FOUNDATION
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9818489	A1	19980507

DESIGNATED STATES
W: AU CA JP AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
APPLICATION INFO.: WO 1997-US19911 A 19971030
PRIORITY INFO.: US 1996-60/029,673 19961030

L5 ANSWER 10 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1996007321 PCTFULL ED 20020514
TITLE (ENGLISH): METHODS FOR MODULATING PROTEIN FUNCTION IN CELLS USING **INTRACELLULAR ANTIBODY** HOMOLOGUES
TITLE (FRENCH): PROCEDES DE MODULATION DE LA FONCTION PROTEINE DANS LES

CELLULES PAR UTILISATION D'HOMOLOGUES D'ANTICORPS INTRACELLULAIRES

INVENTOR(S): CURIEL, David, T.; DESHANE, Jessy

PATENT ASSIGNEE(S): THE UAB RESEARCH FOUNDATION

LANGUAGE OF PUBL.: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9607321	A1	19960314

DESIGNATED STATES
W: CA JP AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE

APPLICATION INFO.: WO 1995-US10740 A 19950823

PRIORITY INFO.: US 1994-8/301,339 19940906
US 1995-8/468,252 19950606

L5 ANSWER 11 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN

ACCESSION NUMBER: 1992019971 PCTFULL ED 20020513

TITLE (ENGLISH): CATIONIZED **ANTIBODIES** AGAINST **INTRACELLULAR** PROTEINS

TITLE (FRENCH): ANTICORPS CATIONISES CONTRE DES PROTEINES INTRACELLULAIRES

INVENTOR(S): MALFROY-CAMINE, Bernard

PATENT ASSIGNEE(S): ALKERMES, INC.; MALFROY-CAMINE, Bernard

LANGUAGE OF PUBL.: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9219971	A1	19921112

DESIGNATED STATES
W: AT AU BB BE BF BG BJ BR CA CF CG CH CI CM CS DE DK ES FI FR GA GB GN GR HU IT JP KP KR LK LU MC MG ML MN MR MW NL NO PL RO RU SD SE SN TD TG US

APPLICATION INFO.: WO 1992-US3566 A 19920430

PRIORITY INFO.: US 1991-693,872 19910430

L5 ANSWER 12 OF 12 PCTFULL COPYRIGHT 2006 Univentio on STN

ACCESSION NUMBER: 1990015822 PCTFULL ED 20020513

TITLE (ENGLISH): MONOCLONAL **ANTIBODY** TO **INTRACELLULAR** EPITOPE OF HUMAN T CELL RECEPTOR ZETA CHAIN AND METHOD OF PREPARATION

TITLE (FRENCH): ANTICORPS MONOCLONAL DE L'EPITOPE INTRACELLULAIRE DE LA CHAINE ZETA DU RECEPTEUR DE CELLULES T HUMAINES ET SON PROCEDE DE PREPARATION

INVENTOR(S): ANDERSON, Paul, J.; SCHLOSSMAN, Stuart, F.

PATENT ASSIGNEE(S): DANA-FARBER CANCER INSTITUTE, INC.

LANGUAGE OF PUBL.: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9015822	A1	19901227

DESIGNATED STATES
W: AT BE CA CH DE DK ES FR GB IT JP LU NL SE

APPLICATION INFO.: WO 1990-US3403 A 19900615

PRIORITY INFO.: US 1989-366,881 19890615

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                                                           ENTRY    SESSION
FULL ESTIMATED COST                                        14.36      14.57

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FILE LAST UPDATED: 5 Feb 2006  (20060205/ED)

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http://www.cas.org/infopolicy.html

=> s ?melanin
L7       10344 ?MELANIN

=> s antibod?
L8      453064 ANTIBOD?

=> s l7 and l8
L9         232 L7 AND L8

=> s cancer? or tumor? or neoplas?
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        416639 TUMOR?
        437398 NEOPLAS?
L10     690038 CANCER? OR TUMOR? OR NEOPLAS?

=> s l10 and l9
L11         43 L10 AND L9

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L12    3481616 IMAGIN? OR TREAT?

=> s l12 and l11
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=> s radio?
L14     626050 RADIO?

=> s l14 and l13
L15          3 L14 AND L13

=> d ibib 1-3

L15  ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2006 ACS on STN
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ACCESSION NUMBER: 2004:888105 CAPLUS
DOCUMENT NUMBER: 142:2821
TITLE: Dead cells in melanoma **tumors** provide abundant antigen for targeted delivery of ionizing radiation by a mAb to **melanin**
AUTHOR(S): Dadachova, Ekaterina; Nosanchuk, Joshua D.; Shi, Li; Schweitzer, Andrew D.; Frenkel, Annie; Nosanchuk, Jerome S.; Casadevall, Arturo
CORPORATE SOURCE: Department of Nuclear Medicine, Albert Einstein College of Medicine, Bronx, NY, 10461, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2004), 101(41), 14865-14870
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:654728 CAPLUS
DOCUMENT NUMBER: 141:186978
TITLE: **Radiolabeled antibodies** for **treatment** of **tumors**
INVENTOR(S): Dadachova, Ekaterina; Nosanchuk, Joshua D.; Casadevall, Arturo
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 23 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004156780	A1	20040812	US 2004-775869		20040210
PRIORITY APPLN. INFO.:			US 2003-446684P	P	20030211

L15 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:636105 CAPLUS
DOCUMENT NUMBER: 135:206479
TITLE: Human G protein-coupled receptors and uses in **treatment** of mental disorder
INVENTOR(S): Vogeli, Gabriel; Wood, Linda S.; Parodi, Luis A.; Lind, Peter
PATENT ASSIGNEE(S): Pharmacia & Upjohn Co., USA
SOURCE: PCT Int. Appl., 279 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001062797	A2	20010830	WO 2001-US5676	20010223
WO 2001062797	A3	20021024		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,				

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            YU, ZA, ZW
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
            DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
            BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 2001041658        A5    20010903    AU 2001-41658          20010222
     EP 1265925           A2    20021218    EP 2001-912924         20010223
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
     US 2003003451        A1    20030102    US 2001-791932         20010223
     US 2005255490        A1    20051117    US 2004-980388         20041102
PRIORITY APPLN. INFO.:                      US 2000-184247P     P  20000223
                                            US 2000-184303P     P  20000223
                                            US 2000-184304P     P  20000223
                                            US 2000-184305P     P  20000223
                                            US 2000-184397P     P  20000223
                                            US 2000-186457P     P  20000302
                                            US 2000-186810P     P  20000303
                                            US 2000-188064P     P  20000309
                                            US 2000-188880P     P  20000313
                                            US 2000-194344P     P  20000403
                                            US 2000-213861P     P  20000623
                                            US 2000-217369P     P  20000711
                                            US 2000-217370P     P  20000711
                                            US 2000-218337P     P  20000714
                                            US 2000-218492P     P  20000720
                                            US 2000-219492P     P  20000720
                                            US 2001-791932      B1 20010223
                                            WO 2001-US5676      W  20010223


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COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                19.94      34.51

FILE 'PCTFULL' ENTERED AT 15:11:02 ON 06 FEB 2006
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FILE LAST UPDATED:         3 JAN 2006      <20060103/UP>
MOST RECENT UPDATE WEEK:       200552        <200552/EW>
FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

>>> UPDATING DELAYED DUE TO DELIVERY FORMAT CHANGES. <<<

>>> NEW IPC8 DATA AND FUNCTIONALITY NOT YET AVAILABLE IN THIS FILE.
    USE IPC7 FORMAT FOR SEARCHING THE IPC. WATCH THIS SPACE FOR FURTHER
    DEVELOPMENTS AND SEE OUR NEWS SECTION FOR FURTHER INFORMATION
    ABOUT THE IPC REFORM <<<

=> s ?melanin
L16       2853 ?MELANIN

=> s antibod?
L17      84196 ANTIBOD?

=> s cancer? or tumor? or neoplas?
         74539 CANCER?
         62442 TUMOR?
         21534 NEOPLAS?
L18      93014 CANCER? OR TUMOR? OR NEOPLAS?
```

```
=> s imagin? or treat?
         73201 IMAGIN?
        326329 TREAT?
L19     363585 IMAGIN? OR TREAT?

=> s radio?
L20     168484 RADIO?

=> s l20 and l19 and l18 and l17 and l16
L21        633 L20 AND L19 AND L18 AND L17 AND L16

=> s anti () ?melanin
        167501 ANTI
           165 ANTIS
        167532 ANTI
                  (ANTI OR ANTIS)
          2853 ?MELANIN
L22          3 ANTI (W) ?MELANIN

=> s l22 and l18
L23          2 L22 AND L18

=> d ibib 1-2

L23    ANSWER 1 OF 2     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:        2004087128 PCTFULL  ED 20041019  EW 200442
TITLE (ENGLISH):         METHYL-&Beta;-ORCINOLCARBOXYLATE FROM LICHEN
                         (EVERNIASTRUM CIRRHATUM) FOR USE FOR THE TREATMENT OF
                         FUNGAL INFECTIONS AND CANCER
TITLE (FRENCH):          METHYL-BETA-ORCINOL-CARBOXYLATE TIRE DU LICHEN
                         EVERNIASTRUM CIRRHATUM DESTINE AU TRAITEMENT
                         D'INFECTIONS FONGIQUES ET DU CANCER
INVENTOR(S):             KHANUJA, Suman, Preet, Singh, Central Institute Of
                         Medicinal And Aromatic Plants, P.O. CIMAP, Lucknow 226
                         015, Uttar Pradesh, IN;
                         TIRUPPADIRIPULIYUR, Ranganathan, Santha, Kumar, Central
                         Institute of Medicinal and Aromatic Plants, P.O. CIMAP,
                         Lucknow 226 015, Uttar Pradesh, IN;
                         GUPTA, Vivek, Kumar, Central Institute of Medicinal and
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                         Pradesh, IN;
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                         Pradesh, IN;
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                         015, Uttar Pradesh, IN;
                         VERMA, Subash, Chandra, Central Institute of Medicinal
                         and Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar
                         Pradesh, IN;
                         SAIKIA, Dharmendra, Central Institute of Medicinal and
                         Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar
                         Pradesh, IN;
                         DAROKAR, Mahendra, Pandurang, Central Institute of
                         Medicinal and Aromatic Plants, P.O. CIMAP, Lucknow 226
                         015, Uttar Pradesh, IN;
                         SHASANY, Ajit, Kumar, Central Institute of Medicinal
                         and Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar
                         Pradesh, IN;
                         PAL, Anirban, Central Institute of Medicinal and
```

Aromatic Plants, P.O. CIMAP, Lucknow 226 015, Uttar Pradesh, IN

PATENT ASSIGNEE(S): COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH, Rafi Marg, New Delhi 110 001, IN [IN, IN]

AGENT: SUBRAMANIAM, Hariharan$, Subramaniam, Nataraj & Associates, E-556 Greater Kailash II, New Delhi 110 048$, IN

LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004087128	A1	20041014

DESIGNATED STATES

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW

RW (ARIPO): GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW

RW (EAPO): AM AZ BY KG KZ MD RU TJ TM

RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR

RW (OAPI): BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2003-IN97 A 20030331

L23 ANSWER 2 OF 2 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2004048547 PCTFULL ED 20040615 EW 200424
TITLE (ENGLISH): INTERMEDIN AND ITS USES
TITLE (FRENCH): INTERMEDINE ET SES UTILISATIONS
INVENTOR(S): HSU, Sheau, Yu Teddy, 2038 Santa Cruz Avenue, Menlo Park, CA 94025, US

PATENT ASSIGNEE(S): THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY, 1705 El Camino Real, Palo Alto, CA 94306-1106, US [US, US]

AGENT: SHERWOOD, Pamela J.$, BOZICEVIC, FIELD & FRANCIS LLP, 200 Middlefield Road, Suite 200, Menlo Park, CA 94025$, US

LANGUAGE OF FILING: English
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2004048547	A2	20040610

DESIGNATED STATES

W: AU CA JP

RW (EPO): AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR

APPLICATION INFO.: WO 2003-US37968 A 20031126
PRIORITY INFO.: US 2002-60/429,327 20021126

=> d kwic 2

L23 ANSWER 2 OF 2 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD . . . intermedin expression in pituitary
sections of rat (G) and bullfrog (H). I and J. Immunohistochemical staining of mouse
pituitary sections using an **anti-melanin**-stimulating
hormone (MSH) antibody (1) or the anti-

intermedin antibody presaturated with an MSH peptide (J). Specific signals are indicated by
arrows. AL,. . .
. . .
peptides and derivatives therefrom also find use in the reduction of edema, for example in rheumatoid arthritis, edema secondary to brain **tumors** or irradiation
for **cancer**, edema resulting from stroke, head trauma or spinal cord injury, post-surgical
edema, asthma and other respiratory diseases and cystoid macular edema.
. .

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=> d his

     (FILE 'HOME' ENTERED AT 15:06:49 ON 06 FEB 2006)

     FILE 'PCTFULL' ENTERED AT 15:07:01 ON 06 FEB 2006
L1         41297 S INTRACELLULAR
L2           276 S L1/TI
L3         84196 S ANTIBOD?
L4          4045 S L3/TI
L5            12 S L4 AND L2
L6             0 S L5 AND (?MELANIN)

     FILE 'CAPLUS' ENTERED AT 15:09:33 ON 06 FEB 2006
L7         10344 S ?MELANIN
L8        453064 S ANTIBOD?
L9           232 S L7 AND L8
L10       690038 S CANCER? OR TUMOR? OR NEOPLAS?
L11           43 S L10 AND L9
L12      3481616 S IMAGIN? OR TREAT?
L13           19 S L12 AND L11
L14       626050 S RADIO?
L15            3 S L14 AND L13

     FILE 'PCTFULL' ENTERED AT 15:11:02 ON 06 FEB 2006
L16         2853 S ?MELANIN
L17        84196 S ANTIBOD?
L18        93014 S CANCER? OR TUMOR? OR NEOPLAS?
L19       363585 S IMAGIN? OR TREAT?
L20       168484 S RADIO?
L21          633 S L20 AND L19 AND L18 AND L17 AND L16
L22            3 S ANTI () ?MELANIN
L23            2 S L22 AND L18

=> s l16/ab
LEFT TRUNCATION IGNORED FOR '?MELANIN' FOR FILE 'PCTFULL'
L24          214 (MELANIN/AB)
Left truncation is not valid in the specified search field in the
specified file.  The term has been searched without left truncation.
Examples: '?TERPEN?' would be searched as 'TERPEN?' and '?FLAVONOID'
would be searched as 'FLAVONOID.'

If you are searching in a field that uses implied proximity, and you
used a truncation symbol after a punctuation mark, the system may
interpret the truncation symbol as being at the beginning of a term.
Implied proximity is used in search fields indexed as single words,
for example, the Basic Index.

=> s l16/clm
LEFT TRUNCATION IGNORED FOR '?MELANIN' FOR FILE 'PCTFULL'
L25          377 (MELANIN/CLM)
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Left truncation is not valid in the specified search field in the specified file. The term has been searched without left truncation. Examples: '?TERPEN?' would be searched as 'TERPEN?' and '?FLAVONOID' would be searched as 'FLAVONOID.'

If you are searching in a field that uses implied proximity, and you used a truncation symbol after a punctuation mark, the system may interpret the truncation symbol as being at the beginning of a term. Implied proximity is used in search fields indexed as single words, for example, the Basic Index.

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L26        475 L24 OR L25

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L27         58 L26 AND L21

=> s l24 and l21
L28         13 L24 AND L21

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        347751 PY>2002
L29         11 L28 NOT PY>2002

=> d ibib 1-5

L29    ANSWER 1 OF 11    PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:       2001098464 PCTFULL  ED 20020826
TITLE (ENGLISH):        CONTINUOUS ADHERENT MELANOCYTE CELL LINE
TITLE (FRENCH):         LIGNEE CELLULAIRE ADHERENTE CONTINUE DE MELANOCYTE
INVENTOR(S):            ALEXANDER, Jeannine;
                        COX, William, I.
PATENT ASSIGNEE(S):     AVENTIS PASTEUR LIMITED;
                        ALEXANDER, Jeannine;
                        COX, William, I.
DOCUMENT TYPE:          Patent
PATENT INFORMATION:
                        NUMBER              KIND     DATE
                        ---------------------------------
                        WO 2001098464         A2 20011227
DESIGNATED STATES
       W:               AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU
                        CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN
                        IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK
                        MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM
                        TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD
                        SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY
                        DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF
                        CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.:      WO 2001-US40540       A  20010418
PRIORITY INFO.:         US 2000-60/213,613       20000622

L29    ANSWER 2 OF 11    PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:       2001007606 PCTFULL  ED 20020828
TITLE (ENGLISH):        AXOR21, A G-PROTEIN COUPLED RECEPTOR
TITLE (FRENCH):         AXOR21, RECEPTEUR COUPLE G-PROTEINE
INVENTOR(S):            DUCKWORTH, David, Malcolm;
                        HILL, Jeffrey;
                        MUIR, Alison, Isobel;
                        SZEKERES, Philip, Graham
PATENT ASSIGNEE(S):     SMITHKLINE BEECHAM PLC
DOCUMENT TYPE:          Patent
PATENT INFORMATION:
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	NUMBER	KIND	DATE
	WO 2001007606	A1	20010201

DESIGNATED STATES
W: JP AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE

APPLICATION INFO.: WO 2000-GB2899 A 20000727
PRIORITY INFO.: GB 1999-9917627.3 19990727
GB 1999-9920046.1 19990824

L29 ANSWER 3 OF 11 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2001001131 PCTFULL ED 20020828
TITLE (ENGLISH): SCREENING METHODS FOR COMPOUNDS THAT AFFECT MELANOGENESIS
TITLE (FRENCH): PROCEDES DE CRIBLAGE DE COMPOSES AYANT UNE INCIDENCE SUR LA MELANOGEN SE
INVENTOR(S): ORLOW, Seth, J.;
MANGA, Prashiela
PATENT ASSIGNEE(S): NEW YORK UNIVERSITY
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2001001131	A1	20010104

DESIGNATED STATES
W: AU CA HU IL JP KR NZ ZA AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE

APPLICATION INFO.: WO 2000-IB861 A 20000627
PRIORITY INFO.: US 1999-60/141,563 19990629

L29 ANSWER 4 OF 11 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2000010507 PCTFULL ED 20020515
TITLE (ENGLISH): USE OF **MELANIN** FOR INHIBITION OF ANGIOGENESIS AND MACULAR DEGENERATION
TITLE (FRENCH): UTILISATION DE MELANINE POUR INHIBER L'ANGIOGENESE ET LA DEGENERESCENCE MACULAIRE
INVENTOR(S): D'AMATO, Robert, J.
PATENT ASSIGNEE(S): THE CHILDREN'S MEDICAL CENTER CORPORATION;
D'AMATO, Robert, J.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 2000010507	A2	20000302

DESIGNATED STATES
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE

APPLICATION INFO.: WO 1999-US19026 A 19990820
PRIORITY INFO.: US 1998-60/097,385 19980821

L29 ANSWER 5 OF 11 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2000009616 PCTFULL ED 20020515
TITLE (ENGLISH): BIOLOGICALLY ACTIVE FRACTION OF VEGETABLE **MELANIN**, PROCESS FOR ITS PRODUCTION AND ITS USE
TITLE (FRENCH): FRACTION BIOLOGIQUEMENT ACTIVE DE MELANINE VEGETALE, SON PROCEDE DE FABRICATION, ET SES UTILISATIONS
INVENTOR(S): KERESTES, Jssn, Jr.;;

	KERESTES, Jssn;;
	VENGER, Ljubov, Andreevna;
PATENT ASSIGNEE(S):	KERESTES, Jssn, Jr.;;
	KERESTES, Jssn;;
	VENGER, Ljubov, Andreevna;
LANGUAGE OF PUBL.:	English
DOCUMENT TYPE:	Patent
PATENT INFORMATION:	

NUMBER	KIND	DATE
WO 2000009616	A1	20000224

DESIGNATED STATES

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SL TJ TM TR TT UA UG US UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.:	WO 1999-SK13	A	19990810
PRIORITY INFO.:	US 1998-PV 1098-98		19980813

=> d kwic 3

L29 ANSWER 3 OF 11 PCTFULL COPYRIGHT 2006 Univentio on STN

ABEN . . . The invention further relates to the pharmacologic and cosmetic uses of such compounds to reduce or increase the synthesis of **melanin** in animal and human melanocytes and melanocyte-derived cells.

DETD . . . function are provided. The invention further relates to methods of using such compounds for the cosmetic and therapeutic reduction or increase of **melanin** content in human and animal cells.

2. Background of the Invention

Melanin is a dark pigment found in plants and animals that protects against ultraviolet radiation and provides decoration in the skin, eyes,. . . and fur of animals (reviewed in Riley, P.A., 1997, Int. J. Biochem. Cell Biol. 11:1235-39). There are two different types of **melanin**.

brown/black **eumelanin** and yellow/red **pheomelanin**. Melanocytes are cells of the epidermis specialized to produce **melanin**. A sophisticated intercellular signaling system determines whether an individual melanocyte will produce **eumelanin** or **pheomelanin** (reviewed in Brilliant, M.H. and Barsh, G.S., 1998, in The Pigmentary System: Physiology and Pathophysiology, 217-29, Oxford University, New York (Nordlund, J.J.. . .

Melanocytes synthesize **melanin** inside of specialized organelles called melanosomes (reviewed in Orlow, S.J., 1998, in The Pigmentary System: Physiology and Pathophysiology, 97-106, Oxford University, New. . .

Defects in the production of **melanin** result in pigmentation deficiencies such as

albinism. Genetic analysis of abnormally pigmented strains of mice has identified more than
60 genes necessary for the normal production of **melanin**
(reviewed in Silvers, W.K., 1979,
The Coat Colors of Mice: A Model for Mammalian Gene Action and Interaction,
Springer-Verlag, Basel). One of these genes encodes the enzyme tyrosinase. Tyrosinase
protein is a multi-functional enzyme that catalyzes several steps in the production of **melanin;**
tyrosinase activities include the rate-limiting steps of converting tyrosine to
dihydroxyphenylalanine (DOPA), and DOPA to dopaquinone (reviewed in Lerner, A.B., and
Fitzpatrick, T.B.,. . .

Another protein that is important for the production of **melanin** is the P protein. In
mice, it is the product of the pink-eye dilution (p) gene. In humans, it is the. . . P protein function suffer from type 11 oculocutaneous albinism
(Durham-Pierre, D., et al., 1994, Nature Genet. 7:176-79). p-null mice produce significantly
less **melanin** than wild-type mice (Silvers, above). A wild-type human P gene, but not a
mutant human P gene, can complement the hypopigmented. . . of p-null mouse
melanocytes (Sviderskaya, E.V., et al., 1997, J. Invest. Dermatol. 108:30-34). P protein is
apparently needed for the production of **eumelanin**, but not of **pheomelanin** (Lamoreux, M.L.,
et aL, 1995, Pigment Cell Res. 8:263-70).

. . .
have suggested that P protein acts as a tyrosine transporter by pumping tyrosine into the melanosome where it is converted into **melanin** by tyrosinase
activity (see, e.g., Rinchik, E.M., et aL, 1993, Nature 361:72-76). First, the P protein bears
some resemblance to transport proteins found in prokaryotes. Second, cultured p-null mutant
mouse melanocytes, which produce much less **melanin** than cultured wild-type mouse
melanocytes, make increased levels of **melanin** when high concentrations of tyrosine are
added to the cellsr growth medium (Sviderskaya, E.V., et al., above; Rosemblat, S. et al.,
1998,. . .

. . .
in melanosomes
(Lamoreux, M.L., et al., above). The integrity of melanosomes is compromised in cells
lacking P protein. Tyrosinase activity, and therefore **melanin** production, is greatly decreased
in these defective melanosornes. Specifically, tyrosinase activity levels in melanocyte
extracts of skin and eyes from p-null mice. . .

Thus, although P protein is known to be critical for the production of normal amounts
of **melanin** in the skin, hair and eyes, the function of the P protein in this process has
remained elusive. Instead, researchers have. . .

. . .

on the discovery that some compounds that inhibit melanogenesis do so by causing a mislocalization of tyrosinase, the key enzyme in **melanin** synthesis.

. . .

have normal or inhibited P protein function, is enzymatically active in the growth or incubation medium, where it can convert tyrosine into **melanin**.

. . .

in these cells is therefore dependent upon P protein function. When cells expressing both heterologous tyrosinase and heterologous P protein are **treated** with drugs that inhibit P protein function such as, for example, imipramine, the tyrosinase activity of these cells is reduced to that. . .

. . .

do not ordinarily express tyrosinase and/or P protein, comprising manipulating these cells so that they express both tyrosinase and P protein, and **treating** the cells with a compound to be tested. The tyrosinase activity of these cells is measured. Compounds that affect (e.g., inhibit or. . .

. . .

provides methods for using, in medicinal 1 0 and cosmetic compositions, compounds that affect or mimic the function of P protein, thereby **treating** a disease, condition, or disorder involving the production (underproduction or overproduction) of **melanin**.

. . .

media or cell extracts were assayed for tyrosine hydroxylase activity, as in FIG. 1. Column 1 , untreated melanocytes; Column 2, melanocytes **treated** with benztropine; Column 3, melanocytes **treated** with 10,11-Dihydro-n,n-dimethyl-5H-dibenz[b,flazepine propanamine (imipramine); Column 4, melanocytes **treated** with 6-Nitro (1-piperazinyl)-quinoline maleate (nitroquipazine). In FIG.

. . .

FIG. 2a.) and nitroquipazine (column 4 in FIG. 2a) is higher than that seen in untreated cells. The extracts from cells **treated** with imipramine (column 3 in FIG. 2a) show a reduced activity. The effects of the drugs on the enzyme activity of. .

.

. . .

first vector carrying a tyrosinase-encoding gene and with a second vector carrying a P protein-encoding gene as in FIG. 3, were **treated** with benztropine, imipramine, nitroquipazine, or left untreated, as in FIG. 2. Cell extracts were prepared as in FIG. 3 The tyrosine. . . cell extracts was determined as in FIG. 1 as a measure of tyrosinase activity. Column 1 , untreated transfectants; Column 2, transfectants **treated** with benztropine; Column 3, transfectants **treated** with imipramine; Column 4, transfectants **treated** with nitroquipazine. Tyrosine

hydroxylase activity is measured in cpm [3H]H20/60 micrograms protein/hr. Cells co-
transfected with a tyrosinase-encoding gene and a. . .

. . .

reduced by
inhibition of cysteinyl proteases. (a) Melan-pl cells incubated in low (0.03 mM) tyrosine and
high (0.3 mM) tyrosine (TYR) were **treated** for 48 hours with increasing concentrations of the
protease inhibitor E64 (pM). The tyrosinase activity in the media is expressed as a
percentage of total activity in the extract and medium. (b) The concentration of **melanin** was
determined by solubilizing the cell pellet and measuring the absorbance at 470 nm.

Yet another aspect of the present invention is based on the finding that melanocytes
treated with compounds that inhibit P protein function accumulate reduced amounts of
intracellular **melanin**, and secrete increased amounts of tyrosinase into the growth medium.

. . .

provides novel methods of screening for
compounds that inhibit melanogenesis. Compounds identified using the methods of the
present invention are useful for **treating** diseases and cosmetic defects associated with the
underproduction or overproduction of **melanin**.

. . .

imipramine, that reduce or eliminate P protein function will have the same effect. Thus, the cellular mislocalization of tyrosinase by
cells **treated** with a test compound indicates that the test compound inhibits melanogenesis. Mislocalization of
tyrosinase resulting in secretion can be detected initially by. . .

. . .

Methods of Screening for Inhibitors of Melanogenesis Using Assays for Tyrosinase activity
Wild-type melanogenic cells grown in in vitro culture will synthesize **melanin** inside of
melanosomes as they do in vivo. In these cultured cells, tyrosinase is found predominantly in
the melanosomal membrane, although some. . . lacks its C-terminal membrane anchor. The secreted tyrosinase,
however, is enzymatically active in the growth or incubation medium where it can synthesize
melanin from extracellular tyrosine. Consequently, tyrosine-containing growth or incubation
media from melanogenic cells that have been inhibited for melanogenesis will turn dark.. . .

. . .

identify compounds that
inhibit or modulate melanogenesis. Melanogenic cells are grown in culture or incubated in
medium containing tyrosine. The cells are **treated** with a test compound. If the test
compound causes tyrosinase to be mislocalized and secreted from the **treated** cells, then
tyrosine in the medium will be converted into **melanin**, darkening the medium. An assay is
used wherein the color of the medium is compared to the color of the medium. . . cells grown or incubated under similar conditions but

without the test compound
(a control medium). If the medium of the cells **treated** with
the test compound turns darker
than the control medium, then the test compound is identified as
candidate for a compound
that. . .
. . .
semi-quantitative data, the media from the
cells is first filtered, centrifuged and/or dialyzed prior to assay for
tyrosinase activity. These
types of **treatments** remove potentially confounding factors
such as cells or particulate matter
(e.g., melanosome or shed membranes) containing tyrosinase that could
compete for
substrate,. . .

Another assay is a **radiometric** assay. In an alternative method
of screening for
compounds that inhibit melanogenesis using this assay, substrate is
radioactively labeled and
added to the growth or incubation medium to be assayed. If tyrosinase is
present in the
medium, it cleaves the substrate into a labeled product and an unlabeled
product. The
amount of **radioactive** substrate that has been converted into
radioactive product is measured.
. . .
concentration of substrate, time of incubation, temperature of
incubation, and other
reaction conditions can be chosen so that the amount of
radioactive product produced is
proportional to the amount of tyrosinase in the growth or incubation
medium being assayed.

A greater amount of labeled product in the medium from cells
treated with the test compound
than in the medium of similar cells grown under similar conditions but
without the test
compound indicates that. . .

An example of this type of assay is the **radiometric** tyrosine
hydroxylase assay. In
this assay, the amount of [3 H]H20 released from [3H]tyrosine as a
result of the tyrosine
hydroxylase. . . Unreacted [3 H]tyrosine is removed from
the medium by adsorption onto 10% (w/v) activated charcoal in 0.1 M
citric acid, then **treated**
with 50% (w/v) Dowex resin solution. The medium is mixed with
scintillant and counted in a
beta-counter. A significant increase in [3 H]H20 levels in the medium of
cells that were **treated**
with a test compound compared to [3 H]H20 levels in the medium of
similar cells grown under
similar conditions without test compound. . .

Yet another example of this type of assay is the **radiometric**
melanin synthesis assay.

In this assay, the amount of [14C]tyrosine or [14 C]DOPA incorporated
into [14C] **melanin** is
measured. In a non-limiting example of a method of screening for
compounds that inhibit
melanogenesis that uses this assay, melanogenic cells. . . 15 minutes

at 40C. The pellet is resuspended in
ice-cold 5% TCA (w/v)..This step is repeated twice. The final pellet
containing [14C]**melanin** is
solubilized in Soluene]-350 (Packard Instrument Company, Meriden, CT)
for four hours,
mixed with scintillant, and counted. Alternatively, the pellet can be
collected on filter paper
and counted. A significant increase in [14C]**melanin** levels in
media of cells that were **treated**
with a test compound compared to [14C] **melanin** levels in media
of similar cells grown under
similar conditions but without the test compound indicates that the test
compound is. . .

. . .
proportional to
the levels of tyrosinase activity in the medium being analyzed. A
significant difference in
fluorescence levels of media from cells **treated** with a test
compound compared to
fluorescence levels of media from similar cells grown under similar
conditions but without the
test compound,. . .

. . .
activity in the medium being analyzed. A significant increase in the
amount of reaction product precipitated from the media of cells
treated with a test compound
compared to the amount of reaction product precipitated from the media
of similar cells grown
under similar conditions. . .

. . .
the art. The
protein detection assays employed herein can be those described in
Harlow and Lane
(Harlow, E. and Lane, D., 1988, **Antibodies**: A Laboratory
Manual, Cold Spring Harbor
Laboratory Press, Cold Spring Harbor, New York), which is incorporated
herein by reference
in its entirety. These assays include, but are not limited to,
immunological assays, including
Western blots, solid-phase **radioimmunoassays**, in situ
hybridizations, and
immunoprecipitations. Anti-tyrosinase **antibodies** are known in
the art, and novel anti-
tyrosinase **antibodies** can be generated using well-known
techniques. Id.

. . .
amount of tyrosinase in the medium is determined using a protein
0 detection assay as described above. Test compounds that cause
treated cells to secrete
more tyrosinase than similar cells grown or incubated under similar
conditions but without the
test compound are candidates for. . .

. . .
found in the melanosomal fraction, or an
increase in the fraction of total tyrosinase protein found in a
non-melanosomal fraction, in cells
treated with the test compound relative to cells not
treated with the test compound indicates
that the test compound inhibits melanogenesis.

Other qualitative assays can be used, such as, e.g., microscopic
examination of cells
treated with the test compound. For example, cell staining

techniques, as known in the art,
can be used. Cells are grown or incubated in medium containing tyrosine and in the presence
of a test compound. The cells are stained using anti-tyrosinase **antibodies**, then examined
microscopically. In a non-limiting example of a method of screening using this type of assay,
melanogenic cells are grown or. . . staining using techniques commonly known in the art. See, e.g., Harlow and
Lane, 1988, above. Prepared cells are stained using anti-tyrosinase **antibodies**. The
anti-tyrosinase **antibodies** can be conjugated to a moiety allowing for its detection. Preferably,
a secondary **antibody** is used. The secondary **antibody** recognizes and binds to the
anti-tyrosinase **antibody**. Preferably, the secondary **antibody** is conjugated to a moiety
allowing for its detection. Alternatively, a tertiary **antibody** can also be used. The tertiary
antibody is preferably conjugated to a moiety allowing for its detection. Examples of moieties
allowing for the detection of **antibodies** include fluorescent molecules (for example,
fluoroscein, rhodamine, Hoechst 33258, or Texas red), enzymes (for example, horseradish
peroxidase, alkaline phosphatase, or beta-galactosidase), gold particles, **radioactive** isotope,
and biotin. An assay is selected based on the labeling moiety used. For example,
fluorescence microscopy can be used to detect fluorescently labeled **antibodies**. For cells
stained with enzyme-conjugated **antibodies**, the cells are further **treated** with an appropriate
substrate for conversion by the **antibody**-bound enzyme, followed by examination by light
microscopy. Gold-particle labeled **antibodies** can be detected using light or electron
microscopy. Isotope-labeled **antibodies** can be detected using radiation-sensitive film. For
cells stained with biotin-conjugated **antibodies**, the cells are further **treated** with streptavidin or
avidin. The streptavidin or avidin is conjugated to a moiety that allows for detection such as,
for example, a fluorescent molecule, an enzyme, gold particles, or **radioactive** isotope.

Preferably, the cells are co-stained with an **antibody** or **antibodies** specific for particular
subcellular compartments (e.g., endosomes, lysosomes, melanosomes, etc.). Using any one
of these techniques, or any other known technique for detecting **antibodies** in
antibody-stained cells, the subcellular distribution of tyrosinase can be determined. If the test
compound causes an increased amount of tyrosinase to be. . .
. . .
selected that allows the
length and/or mass of tyrosinase protein to be determined. For example, Western blots or
other immunohistochernical techniques using **antibodies** that recognize the N-terminal or
central portions of the tyrosinase protein, or other standard molecular biological techniques

useful for the determination of protein length or mass, can be performed on extracts of these
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cells and/or on their growth or incubation medium. **Antibodies** appropriate for these assays
can be prepared using standard immunological techniques. See, e.g., Harlow and Lane,
1988, above. If the assay reveals. . . under similar conditions but without the
test compound, then the test compound inhibits melanogenesis. Alternatively, Western blots
or other immunohistochemical techniques using **antibodies** recognizing the C-terminal portion
of tyrosinase (e.g., the anti-PEP7 **antibody** prepared as described in Jimenez et aL, 1991, J.
. . .
266:1147-1156) can be used in the assay. In these assays, a reduction in the
amount of tyrosinase protein detected by the **antibodies** indicates that the test compound
inhibits melanogenesis, because the truncated tyrosinase lacks the sequences recognized by
the **antibodies**.
. . .
or a membrane (e.g.,
nitrocellulose) is soaked in L-DOPA and applied to the gel. Active tyrosinase in the gel
converts L-DOPA into **melanin**, creating dark spots on the filter or membrane indicating the
location, and therefore the relative size, of tyrosinase. If cells **treated** with the test compound
produce two spots on the filter or membrane, wherein one spot indicates tyrosinase of the
same size as. . .
. . .
The ratio of soluble tyrosinase in the soluble fraction to insoluble, membrane-bound tyrosinase in the membrane fraction is determined. If cells **treated** with the
test compound have higher levels of soluble tyrosinase than insoluble, membrane-bound
tyrosinase than that from similar cells grown under similar. . .
. . .
are denser than immature
melanosomes, and so can be separated from them on the basis of density using well known
techniques. Cells **treated** with a test compound that have melanosomes that are altered in
number, size, shape, and/or color compared to melanosomes from similar.
. .
. . .
gene, tyrosinase is predominantly secreted or found in non-melanosomal vesicles. Inhibition of melanogenesis and the mislocalization of tyrosinase can be mimicked
by **treating** wild-type melanocytes with compounds that inhibit the function of P protein (e.g.,
imipramine).
. . .
or incubation
medium of the cells can be measured. For example, tyrosine can be added to the medium,
and its conversion to **melanin** monitored. Alternatively, non-tyrosine or altered tyrosine
substrates of tyrosinase can be added to the medium, and their

conversion into reaction
products by tyrosinase can be followed by, for example, colorimetric assays (e.g., the DOPA
oxidase assay), **radiometric** assays (e.g., the
radiometric hydroxylase or **radiometric melanin**
synthesis assays), fluorescence assays, or by the precipitation of reaction products. These
assays are described in detail in Section 5 1.1, above.

. . .
may be used. These assays can
measure, for example, the amount of tyrosinase in the growth or incubation medium of the
cells **treated** with the compound to be tested, the cellular localization of tyrosinase (e.g., by
subcellular fractionation of the cells, or by staining. . .

. . .
of P protein function. For example, these assays can measure the amount or
activity of TRP-1 and/or TRIP-2 protein in cells **treated** with the compound to be tested, the
abundance or composition of the high molecular weight melanogenic complex, or the
presence or absence. . .

. . .
well
known in the art (and, in part, illustrated below by way of non-limiting example), as are their
amino acid structures and **antibodies** that recognize the same.
For example, one can assay
for the presence and/or levels of lysosomal hydrolases in whole cells or cell extracts, in the
large granule fraction of a cell extract, and/or in the medium from cells **treated** with test
compounds. Compounds that cause either a decrease in accumulation of such lysosomal
enzymes in cells or, more particularly, the large. . .

Alternatively, melanogenic cells that do not contain P protein are **treated** with the compound
to be tested, and the amount of tyrosinase secreted into the medium is assayed. If the
amount of tyrosinase in the medium from melanogenic cells that do not contain P protein
(e.g., melan-p cells) decreases when the cells are **treated**
with the test compound, then the
test compound is a candidate for a compound that mimics P protein function. Tyrosinase
activity in. . . example, by using any of the techniques
described above. For example, tyrosine can be added to the medium, and its conversion to
melanin monitored.

. . .
be used. These assays can measure,
for example, the amount of tyrosinase in the growth or incubation medium of the cells **treated**
with the compound to be tested, the cellular localization of tyrosinase (e.g., by subcellular
fractionation of the cells, or by staining and. . .

. . .
and/or an increase in
melanogenesis. For example, these assays can measure the amount of TRP-1 and/or TRP-2
protein or activity in cells **treated** with the compound to be

tested, the abundance or
composition of the high molecular weight melanogenic complex, or the
presence or. . .
. . .
is also determined. The ratio of intracellular tyrosinase to
secreted tyrosinase is then calculated. If this ratio is higher for
cells **treated** with the
compound to be tested than for similar cells grown under similar
conditions but without the
compound, then the compound increases. . . in medium containing the
compound to be tested, and the ratio of
intracellular tyrosinase to secreted tyrosinase is higher for cells
treated with the compound
than for untreated cells, then the compound can mimic P protein
function, and thereby
increase melanogenesis.
. . .
cells that do not contain
melanosomes. However, non-melanogenic cells can be made to express both
P protein and
tyrosinase, and to synthesize **melanin**. For purposes of the
present invention, the term cells
made to express both P protein and tyrosinase/' is defined as cells. .
.
. . .
express both tyrosinase and P protein is
sensitive to the action of compounds that inhibit P protein function.
Wherf these cells are
treated with, for example, imipramine, the tyrosinase activity
of these cells is markedly
reduced. The effect of these compounds on tyrosinase activity. . .
. . .
of extracts of these cells is measured. Tyrosinase activity can be
measured using any of the assays discussed above, including the
radiometric tyrosine
hydroxylase assay, colorimetric DOPA oxidase assay, the DHICA converting
assay, an assay
for the ability to convert [14C]DOPA into TCA precipitable material, or
by any other method
known in the art. If the tyrosinase activity of the extracts of cells
treated with the test
compound is lower than the tyrosinase activity of the extracts of
similar cells grown under
similar conditions but without. . . tyrosinase but not P protein,
then the compound decreases P protein function. Conversely, if the
tyrosinase activity of the
extracts of cells **treated** with the test compound is higher
than the tyrosinase activity of the
extracts of similar cells grown under similar conditions but. . .
. . .
made to express
tyrosinase and P protein exploits, in part, the discovery that these
cells, if incubated long
enough, turn black with **melanin** deposition. Cells expressing
tyrosinase and P protein, or
tyrosinase but not P protein, are **treated** with a compound to
be tested. The cells are
incubated for a period of time sufficient to allow cells expressing both
tyrosinase and P
protein, but which are not **treated** with the test compound, to
accumulate **melanin**. The
melanin content of **treated** and untreated cells can
be assayed by visual inspection or

spectrophotometric analysis of the cells, or by using other techniques well known in the art. If the **melanin** content of the cells expressing both tyrosinase and P protein and **treated** with the test compound is lower than the **melanin** content of similar cells not **treated** with the compound, then the compound can decrease melanogenesis. If the **melanin** content of cells expressing tyrosinase but not P protein is not substantially altered by the presence or absence of the compound, then the compound inhibits P protein function. Conversely, compounds that cause an increase in **melanin** formation in these cells, relative to similar cells grown under similar conditions but without the compound, increase melanogenesis. If the compound also fails to increase **melanin** formation in non-melanogenic cells expressing a tyrosinase-encoding gene but not a P protein-encoding gene, then the compound increases P protein function.

Cell. Biol. 7:1436-1444); the mouse mammary **tumor** virus control region, which is active in testicular, breast, lymphoid and mast cells (Leder et aL, 1986, Cell 45:485-495); the albumin gene. . .

. . .

the primary method of screening is based on the identification of compounds that lower the activity of tyrosinase or the amount of **melanin** produced, or that lower the amount of tyrosinase secreted. Direct inhibitors of tyrosinase will also cause a reduction in the activity of tyrosinase and the amount of **melanin** produced, or can cause a reduction in tyrosinase activity, but would not necessarily affect P protein function.

. . .

can be tested for direct binding to purified P protein in vitro, or by copurification with P protein from P protein-expressing cells **treated** with the compound. Each of these methods of screening can determine whether the compound binds directly to P protein. A compound. . .

. . .

chemical analogs of irnipramine. As described above, imipramine inhibits P protein function. Irnipramine is a tricyclic tertiary amine used in the **treatment** of depression. See Gilman, A.G. et aL, eds, 1990, Goodman and Gilmanfs The Pharmacological Basis of Therapeutics, Eighth Edition, 405-14, Pergamon Press, New York. Other tricyclic tertiary amines used in the **treatment** of depression such as, for example, amitriptyline, trimipramine, or doxepin (see id.) can be test compounds in screens for compounds that affect P protein function. Secondary amines used in the **treatment** of depression such as, for example, desipramine, nortriptyline, protriptlyine, amoxapine, or maprotiline (see id.) also are preferred compounds for the screens of. . .

. . .
Inhibiting, Increasing or Mimicking P Protein Function
Compounds that affect or mimic the function of P protein can be used to **treat** animals
or, preferably, humans that have diseases, conditions, or disorders caused by the production
or overproduction of **melanin**. Such diseases, conditions, or disorders include those that can
be characterized by discolorations of the skin or hair such as, for. .
.

Compounds that increase the function of P protein or that mimic the function of P protein can
be used to **treat** animals or, preferably, humans that have diseases, conditions, or disorders
caused by the underproduction of **melanin** such as, for example, post-inflammatory
hypopigmentation, pityriasis alba, and certain forms of albinism such as, for example, OCA 11
albinism. Additionally, such. . .

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For the purposes of this application, the terms **treatmentf**, therapeutic use, and
%,medicinal use shall refer to any and all uses of the compositions of the invention which
remedy a disease. . .
. . .
administered to a patient, person, or animal
having a disease, disorder, or condition which is of a type that produces, or overproduces,
melanin.

The amount of compound that affects or mimics P protein function which will be
effective in the **treatment** of a particular disease, disorder, or condition will depend on the
nature of the disease, disorder, or condition, and can be. . . clinical
techniques. Where possible, it is desirable to determine in vitro the cytotoxicity of the
compound to the tissue type to be **treated**, and then in a useful animal model system prior to
testing and use in humans.

The compounds that affect or mimic P protein function can be administered for the
reduction or increase of **melanin** synthesis by any means that results in contact of the active
agent with its site of action in the body of. . .

Occurrences in the skin or hair of noticeable but undesired pigmentation as a result of
melanin production, overproduction or underproduction can be **treated** using the methods of
the present invention.

5 3 Endpoints and Dosages
An effective dosage and **treatment** protocol can be determined by conventional
means, starting with a low dose in laboratory animals and then increasing the dosage while
monitoring. . .

. . .
of the patient, the age of the patient, the general condition of the patient, the particular disease, condition, or disorder being **treated**, the severity of the disease, condition, or disorder being **treated**, the presence of other drugs in the patient, the effect desired, and the like. The trial dosages would be chosen after. . .

. . .
art will appreciate that the endpoint chosen in a particular case will vary according to the disease, condition, or disorder being **treated**, the outcome desired by the patient, subject, or **treating** physician, and other factors. Where the composition is being used to lighten or darken skin color such as, for example, to. . . For example, endpoints can be defined subjectively such as, for example, when the subject is simply I]satisfiedfl with the results of the **treatment**. For pharmacological compositions, the endpoint can be determined by the patient, s, or the **treating** physician, s, satisfaction with the results of the **treatment**. Alternatively, endpoints can be defined objectively. For example, the patient, s or subject, s skin or hair in the **treated** area can be compared to a color chart. **Treatment** is terminated when the color of the skin or hair in the **treated** area is similar in appearance to a color on the chart. Alternatively, the reflectance of the **treated** skin or hair can be measured, and **treatment** can be terminated when the **treated** skin or hair attains a specified reflectance.

Alternatively, the **melanin** content of the **treated** hair or skin can be measured. **Treatment** can be terminated when the **melanin** content of the **treated** hair or skin reaches a specified value.

Melanin content can be determined in any way known to the art, including by histological methods, with or without enhancement by stains for **melanin**.

Preferred agents are those that are viscous enough to remain on the **treated** area, those that do not readily evaporate, and/or those that are easily removed by rinsing with water, optionally with the aid of. . .

. . .
(ala, PIP), an immortalized melanocyte line derived from C57BL16J mice wildtype at the p locus (Bennett et al., 1987, Int. J. **Cancer** 39:414-418), were maintained in culture in Dulbecco's modification of Eagle's medium (DIVIE). Melan-pll melanocytes from mice lacking all p gene transcripts due. . .

. . .
0.03 mM tyrosine for low tyrosine conditions or 0.3 mM tyrosine for high tyrosine conditions (Bennett, D.C. et al., 1987, Int. J. **Cancer** 39:414-418), (Sviderskaya et al., , J. Invest. Dermatol. 108:30-34). Aliquots of culture medium were withdrawn, dialyzed against 0.1 M sodium phosphate buffer, pH 6.8, and analyzed for tyrosinase activity using a **radiometric** tyrosine

hydroxylase assay (Orlow, S.J. et
al., 1990, J. Invest. Dermatol. 94:461-64).

For **treatment** with test compounds, cultured melan-a
melanocytes were incubated for
48 hours in the presence of low tyrosine in the medium as. . .

Treatment with benztropine did not alter the levels of
tyrosinase activity secreted to
the incubation medium of melan-a cells (FIG. 2). **Treatment**
with either imipramine or
nitroquipazine significantly increased the levels of tyrosinase activity
found in the cells'
incubation medium (FIG. 2).

6.3 Discussion
Melan-a cells are melanocytes derived from wildtype mice. They have
fully functional
P protein and tyrosinase, and produce **melanin**. Melan-p cells,
however, are derived from
p-null mice having a deletion of the entire p gene coding sequence.
Thus, they produce no P
protein. Consequently, melan-p cells have lower tyrosinase activity and
make less **melanin**
than melan-a cells.

. . .
are genetically altered to reduce or
eliminate P protein function, as in melan-p cells (FIG. 1), or when the
cells are **treated** with a
compound that inhibits P protein function, such as imipramine (FIG. 2b).

. . .
5OmM Tris-HCI (pH 7.4), 2mM EDTA,
150 rnM NaCl and 1% Triton X Cell extracts were analyzed for tyrosinase
activity using
a **radiornetric** tyrosine hydroxylase assay (Orlow, S.J. et al.,
1990, above).

. . .
with a vector carrying a tyrosinase-encoding gene, or with
vectors carrying a tyrosinase-encoding gene and a P protein-encoding
gene as above, were
treated with benztropine, or imipramine, or nitroquipazine, or
left untreated, as above, and cell
extracts were then prepared as above. The tyrosinase. . .

7.2 Results
As shown in FIG. 2a, extracts from melan-a cells **treated** with
benztropine or
nitroquipazine had greater tyrosinase activities than untreated cells.
Extracts from cells
treated with irniprarnine had less tyrosinase activity than
untreated cells.

. . .
inhibit P protein function. Melan-a
cells are wildtype for the P protein-encoding gene. Yet extracts taken
from these cells after
they are **treated** with imipramine have lower tyrosinase
activity than untreated melan-a cells
(FIG. 2). In contrast, extracts from cells **treated** with
benztropine or nitroquipazine have
higher tyrosinase activity than untreated cells (FIG. 2).

. . .
can produce what might be
considered an %%artificial melanocyte./f These cells express active

tyrosinase and P protein
(FIG. 3), and even produce **melanin**. Cotransfection of COS
cells with both a tyrosinase-
encoding gene and a P protein-encoding gene produces cells with
approximately four times
more. . .

Extracts from COS cells that have been transformed with both a
tyrosinase-encoding
gene and a P protein-encoding gene and then **treated** with
imipramine contained only about
one third of the tyrosinase activity of similar cells not
treated with imipramine (FIG. 4). The
tyrosinase activity of COS cells that were transfected with only a
tyrosinase-encoding gene
and then **treated** with imipramine was not significantly
different than the tyrosinase activity of
extracts of similar cells not **treated** with imipramine (FIG.
4). These results indicate that
imipramine reduces tyrosinase activity by inhibiting P protein function.
By contrast,
benztropine did not. . .

If proteolysis and secretion of tyrosinase were the precipitating factor
in the misrouting
of tyrosinase, then E64 should increase **melanin** accumulation
in melan-pl cells. The effects
of E64 were further investigated, and a potential synergy with tyrosine,
which also reduced
secretion into. . .

The higher concentration of E64 was not more effective. Surprisingly,
E64 reduced
intracellular **melanin** production at high concentrations of
tyrosine. Thus, despite its ability to
diminish proteolysis and secretion of tyrosinase from melan-pl cells,
E64 was not able to
cause tyrosinase to re-route to the melanosome and begin **melanin**
synthesis and deposition.

. . .
cells
were incubated in 0. 1 % 1 -DOPA twice for 2.5 hours. The cells were
washed 3 times in buffer
and **treated** with 1.0% osmium tetroxide containing 1.5%
potassium ferrocyanide (Karnovsky,
1971) for 30 minutes. The cells were washed, stained en bloc with. . .

. . .
Golgi network (TGN) and in 50 nrn vesicles which were confined to the
vicinity of the
Golgi apparatus (FIG. 7a). DOPA **treated** melan-pl cells also
demonstrated reaction product
in the TGN and neighboring 50 nm vesicles (FIG. 7b). In addition,
reaction product was
present. . .

CLMEN 1 . A method of screening for compounds that inhibit melanogenesis, the
method
comprising: **treating** cells expressing a tyrosinase-encoding
gene with a test compound, and
determining the cellular localization of tyrosinase in the presence of
the. . .

18 A method of screening for compounds that increase melanogenesis

comprising: **treating** cells expressing a tyrosinase-encoding gene with a test compound, and
determining the amount of tyrosinase secreted by the cells in the. . .

25 The method of claim 23 or 24, wherein the cells are visually examined for an
increase in **melanin** production.

31 The method of claim 26, wherein the cells are visually examined for an
increase in **melanin** production.

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L29 ANSWER 6 OF 11 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1999006074 PCTFULL ED 20020515
TITLE (ENGLISH): USE OF TEXAPHYRINS IN DETECTION OF **MELANIN** AND **MELANIN** METABOLITES OF MELANOTIC MELANOMA
TITLE (FRENCH): UTILISATION DE TEXAPHYRINES DANS LA DETECTION DE LA MELANINE ET DES METABOLITES DE LA MELANINE DU MELANOME MELANIQUE
INVENTOR(S): WOODBURN, Kathryn, W.;
YOUNG, Stuart, W.
PATENT ASSIGNEE(S): PHARMACYCLICS, INC.;
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APPLICATION INFO.: WO 1998-US15833 A 19980729
PRIORITY INFO.: US 1997-08/903,099 19970730

L29 ANSWER 7 OF 11 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1997000892 PCTFULL ED 20020514
TITLE (ENGLISH): DEPIGMENTING ACTIVITY OF AGOUTI SIGNAL PROTEIN AND PEPTIDES THEREOF
TITLE (FRENCH): ACTIVITE DE DEPIGMENTATION DE LA PROTEINE-SIGNAL D'AGOUTI ET SES PEPTIDES
INVENTOR(S): HEARING, Vincent, J., Jr.
PATENT ASSIGNEE(S): THE GOVERNMENT OF THE UNITED STATES OF AMERICA, represented by THE SECRETARY DEPARTMENT OF HEALTH AND HUMAN SERVICES;
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MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM
TR TT UA UG US UZ VN KE LS MW SD SZ UG AM AZ BY KG KZ
MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC
NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1996-US10695 A 19960621
PRIORITY INFO.: US 1995-60/000,436 19950623

L29 ANSWER 8 OF 11 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1994022468 PCTFULL ED 20020513
TITLE (ENGLISH): METHOD FOR DELIVERING BENEFICIAL COMPOSITIONS TO HAIR FOLLICLES
TITLE (FRENCH): PROCEDE PERMETTANT L'APPORT AUX FOLLICULES PILEUX DE COMPOSITIONS PROFITABLES
INVENTOR(S): LI, Lingna;
LISHKO, Valeryi, K.
PATENT ASSIGNEE(S): ANTICANCER, INC.;
LI, Lingna;
LISHKO, Valeryi, K.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9422468	A1	19941013

DESIGNATED STATES
W: AU CA CN JP KR US AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
APPLICATION INFO.: WO 1994-US3634 A 19940401
PRIORITY INFO.: US 1993-8/041,553 19930402
US 1994-8/181,471 19940113

L29 ANSWER 9 OF 11 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1992018166 PCTFULL ED 20020513
TITLE (ENGLISH): **MELANIN**-BASED AGENTS FOR IMAGE ENHANCEMENT
TITLE (FRENCH): AGENTS A BASE DE MELANINE UTILISES POUR LE REHAUSSEMENT DES IMAGES
INVENTOR(S): WILLIAMS, Robert, F.
PATENT ASSIGNEE(S): BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM;
WILLIAMS, Robert, F.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9218166	A1	19921029

DESIGNATED STATES
W: AT AU BB BE BF BG BJ BR CA CF CG CH CI CM CS DE DK ES FI FR GA GB GN GR HU IT JP KP KR LK LU MC MG ML MN MR MW NL NO PL RO RU SD SE SN TD TG US
APPLICATION INFO.: WO 1992-US3177 A 19920415
PRIORITY INFO.: US 1991-685,937 19910415

L29 ANSWER 10 OF 11 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1992007580 PCTFULL ED 20020513
TITLE (ENGLISH): THERAPEUTIC USES OF **MELANIN**
TITLE (FRENCH): UTILISATIONS THERAPEUTIQUES DE LA MELANINE
INVENTOR(S): BERLINER, David, L.;
ERWIN, Robert, L.;
McGEE, David, R.
PATENT ASSIGNEE(S): BIOSOURCE GENETICS CORPORATION
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent

PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9207580	A1	19920514

DESIGNATED STATES
W: AT AU BE CA CH DE DK ES FI FR GB GR IT JP LU NL NO SE
APPLICATION INFO.: WO 1991-US8213 A 19911105
PRIORITY INFO.: US 1990-609,311 19901105

L29 ANSWER 11 OF 11 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1990011295 PCTFULL ED 20020513
TITLE (ENGLISH): **MELANIN**-CONCENTRATING HORMONES AND METHODS OF **TREATMENT** USING SAME
TITLE (FRENCH): HORMONES CONCENTRANT LA MELANINE ET PROCEDES DE TRAITEMENT UTILISANT DE TELLES HORMONES
INVENTOR(S): VAUGHAN, Joan;
FISCHER, Wolfgang, Hermann;
RIVIER, Jean, Edouard;
NAHON, Jean-Louis, Marie;
PRESSE, Francoise, Genevieve;
VALE, Wylie, Walker, Jr.
PATENT ASSIGNEE(S): THE SALK INSTITUTE FOR BIOLOGICAL STUDIES
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

	NUMBER	KIND	DATE
	WO 9011295	A1	19901004

DESIGNATED STATES
W: AT BE CA CH DE DK ES FR GB IT JP LU NL SE
APPLICATION INFO.: WO 1990-US1492 A 19900320
PRIORITY INFO.: US 1989-326,984 19890322